



Long-Duration Space Flight and the Microgravity Ocular Syndrome (MOS)

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Houston, TX



Why We Do What We Do...





Recent Headlines:

Speaking of Science

Too much space travel is hazardous for your eyeballs

Light Bad for Astronauts' Vision, Study Suggests

By SPACE.com Staff | March 13, 2012 12:00am ET

Possible Mars Mission 'Showstopper': Vision Risks for Astronauts

By Mike Wall, Senior Writer | April 8, 2014 07:00am ET



Health & Science

The mysterious syndrome impairing astronauts' sight

Astronauts' eyes are at risk after too much time in space

Astronauts Returning to Earth With Vision Problems

The Washington Post

POST ORIGINALS · July 8, 2016

Space travel is causing visual impairment for some astronauts. Will this prevent travel to Mars?

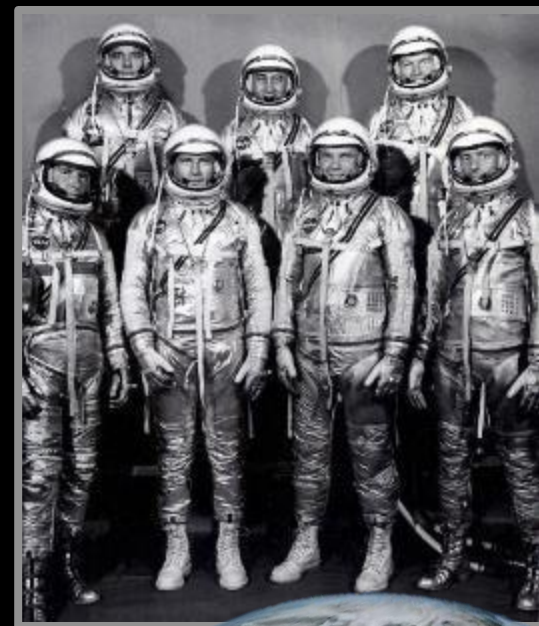
A mission to Mars
Credit: ESA

astronauts
vision



Background: *The Space Environment*

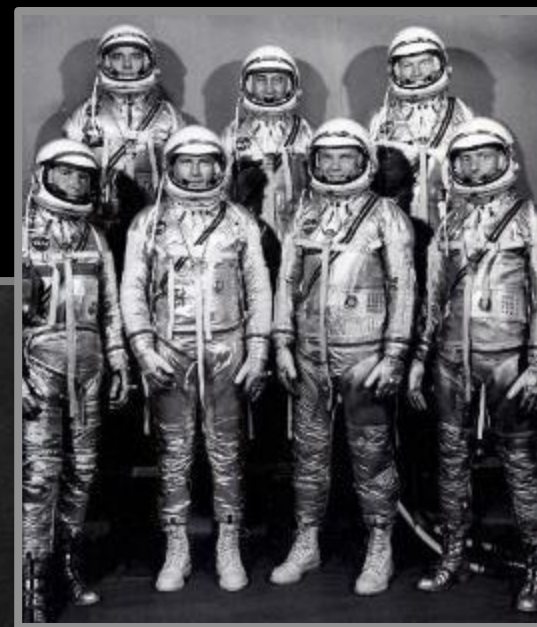
- Bottom-line: Not human friendly. For example...
 - **Vacuum**: No atmosphere; no air
 - Gravity
 - Holds Earth in orbit w/ sun, and moon in orbit around Earth
 - Gravity reduces w/ distance. ISS (@ ~200-250 mi) feels 90% of Earth's gravity...But...
 - ISS moves at ~17,500 mph, in constant freefall = **"Microgravity"**
 - **Temperature extremes**
 - **Ionizing (high energy) radiation**: Galactic cosmic rays, solar proton events
 - Orbiting **space junk/debris**: >550K larger than 1cm





Background: *U.S. Space Flight*

- “We choose to go to the moon...”
 - **Mercury**
 - $n = 6$
 - Duration: 15m to 1.5d



* Person flights; may include multiple-time flyers w/in program



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Background: *U.S. Space Flight*

- “We choose to go to the moon...”

- **Mercury**

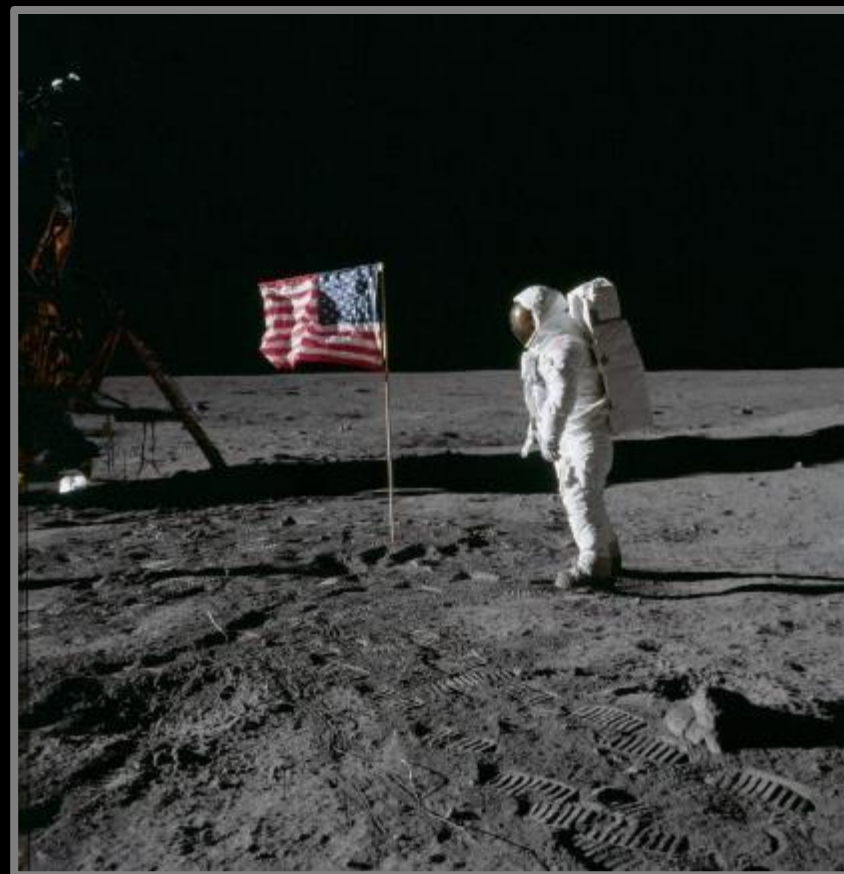
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Background: *U.S. Space Flight*

■ Skylab

- $n = 9$
- Duration: 28 to 84d



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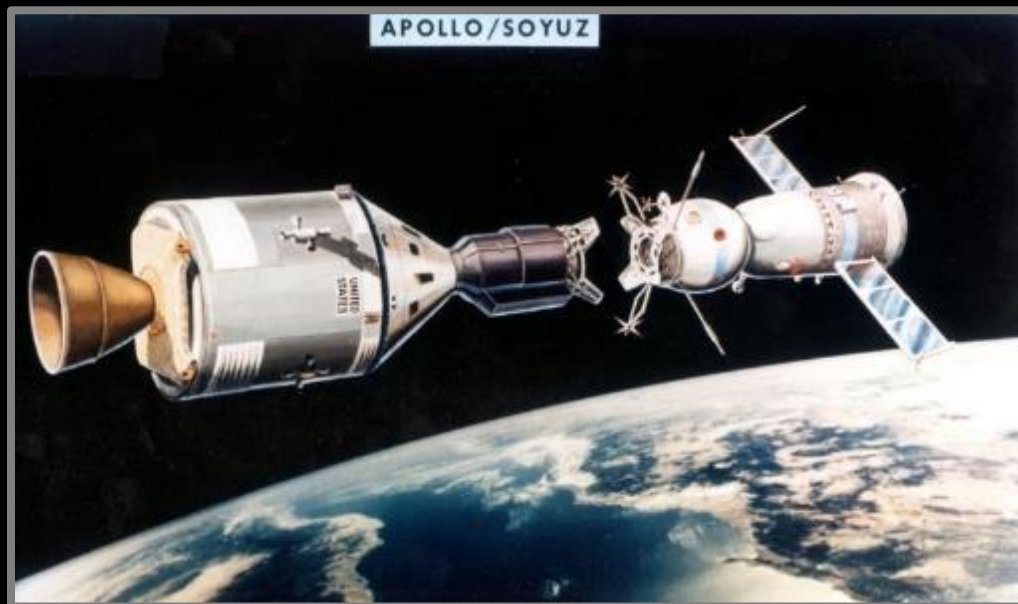
Background: *U.S. Space Flight*

■ Skylab

- $n = 9$
- Duration: 28 to 84d

■ Apollo-Soyuz

- $n = 3$
- Duration: 9d



* Person flights; may include multiple-time flyers w/in program



Background: *U.S. Space Flight*

- **Skylab**
 - $n = 9$
 - Duration: 28 to 84d
- **Apollo-Soyuz**
 - $n = 3$
 - Duration: 9d
- **Space Shuttle**
 - * $n = 710$
 - Duration: ~2wk



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Background: *U.S. Space Flight*

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 - $n = 9$
 - Duration: 28 to 84d
- **Apollo-Soyuz**
 - $n = 3$
 - Duration: 9d
- **Space Shuttle**
 - $*n = 710$
 - Duration: ~2wk
- **Shuttle-Mir**
 - $n = 7$
 - Duration: ~0.5yr



* Person flights; may include multiple-time flyers w/in program



Background: *U.S. Space Flight*

■ International Space Station

- In use since 2000
- *n = 58 (as of 31 Jan 17)
- Duration: ~0.5 to 1y
- International partners
 - United States
 - Russia
 - European Union
 - Canada
 - Japan
- Crew: Typically 5-6
- “Low Earth orbit”

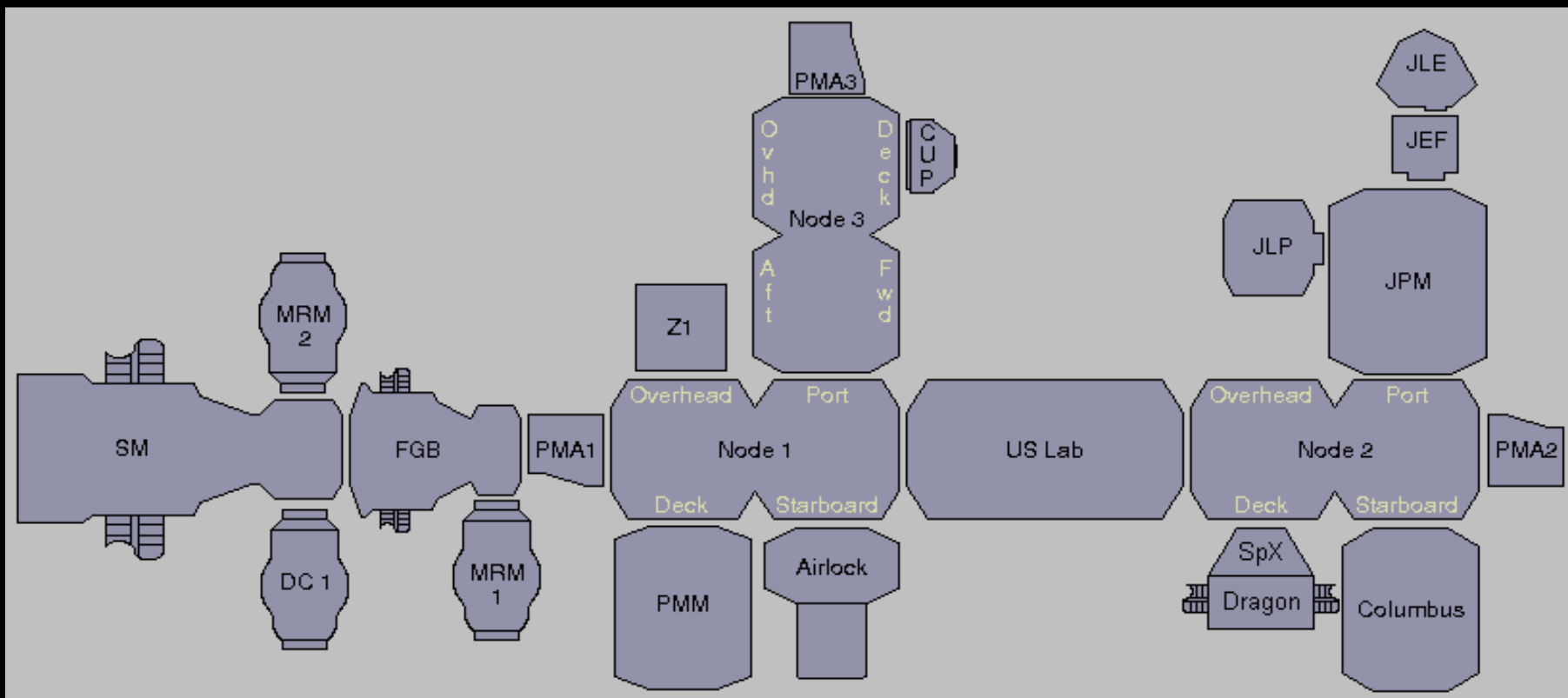


* Person flights; may include multiple-time flyers w/in program



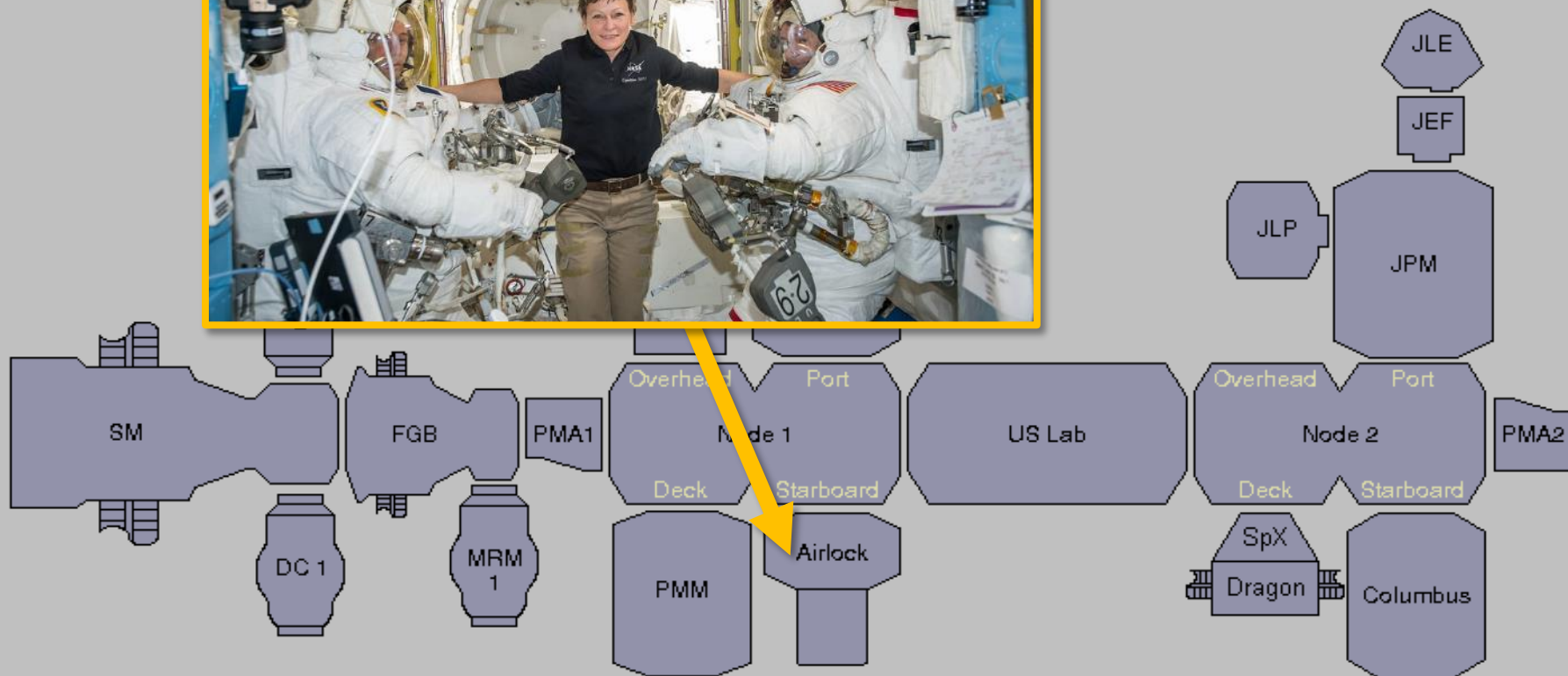
Background: *U.S. Space Flight*

- International Space Station



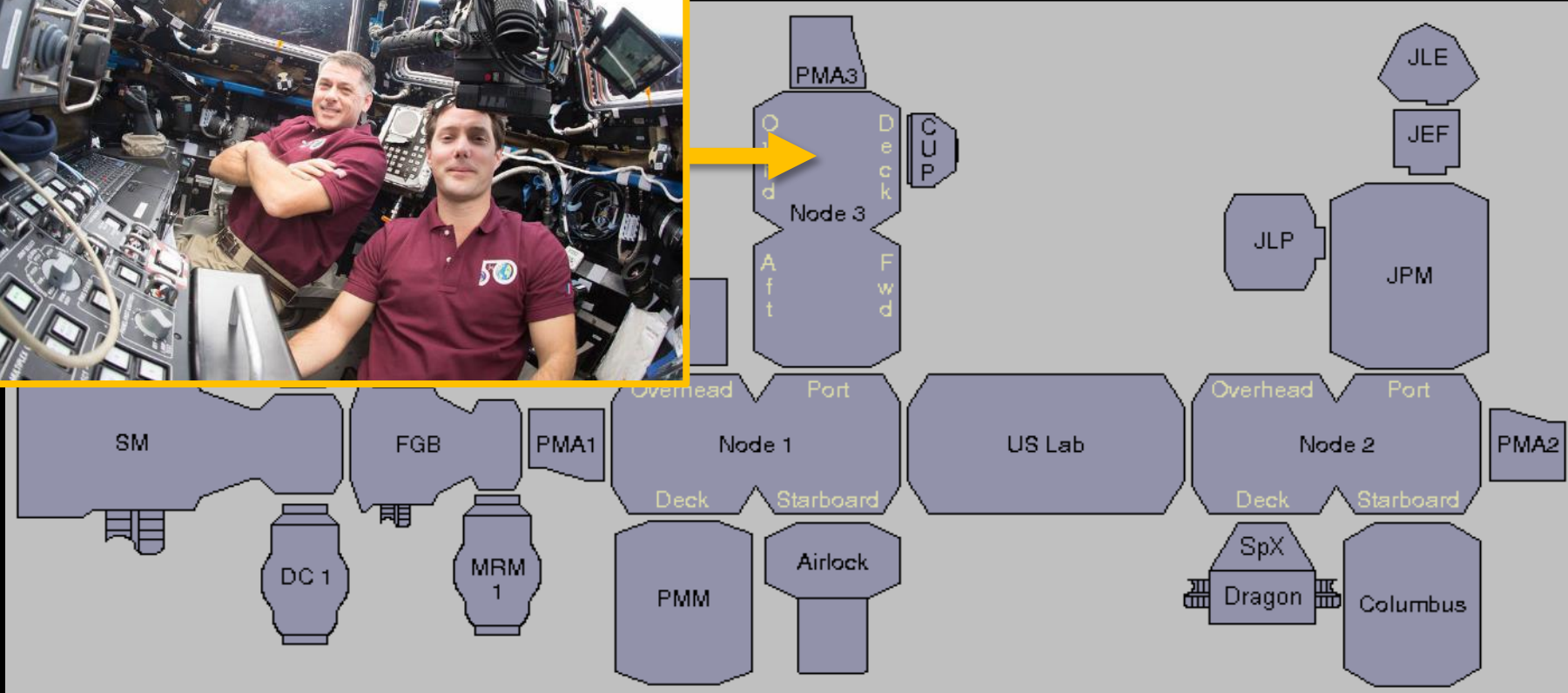


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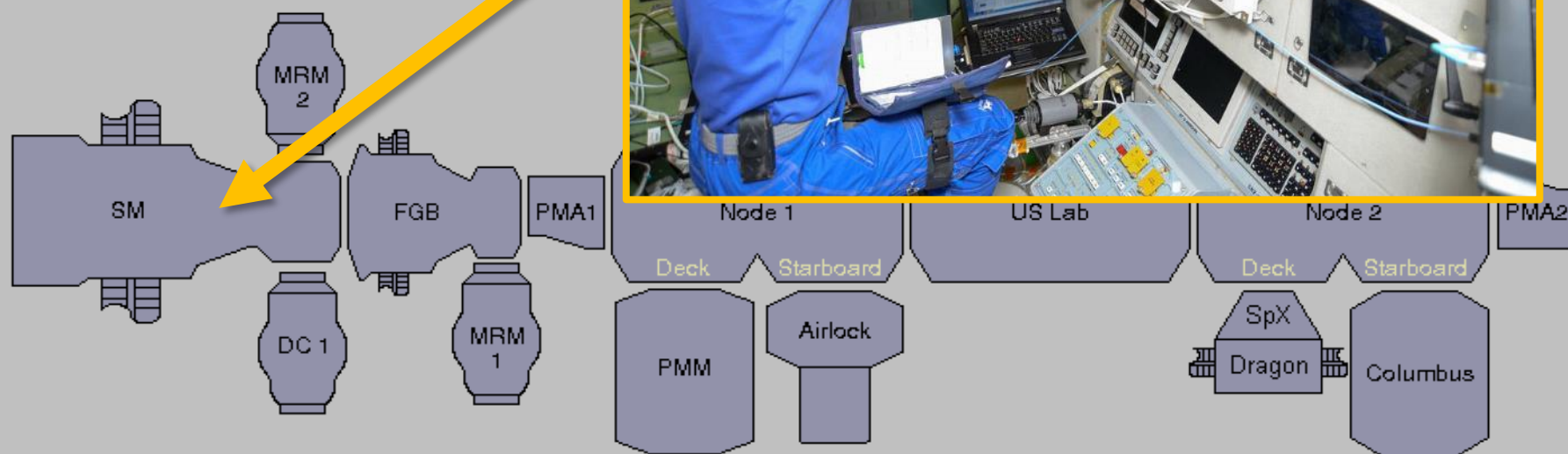


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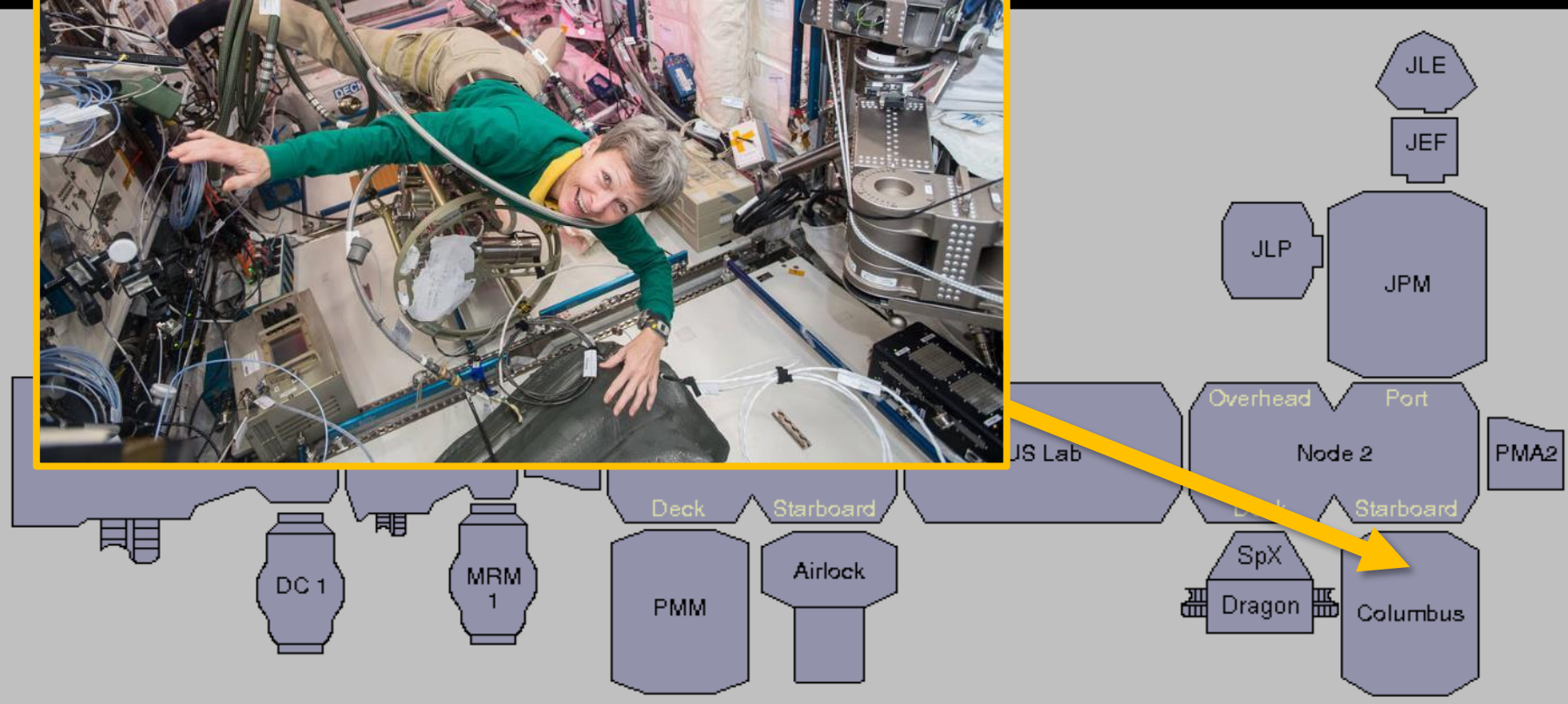


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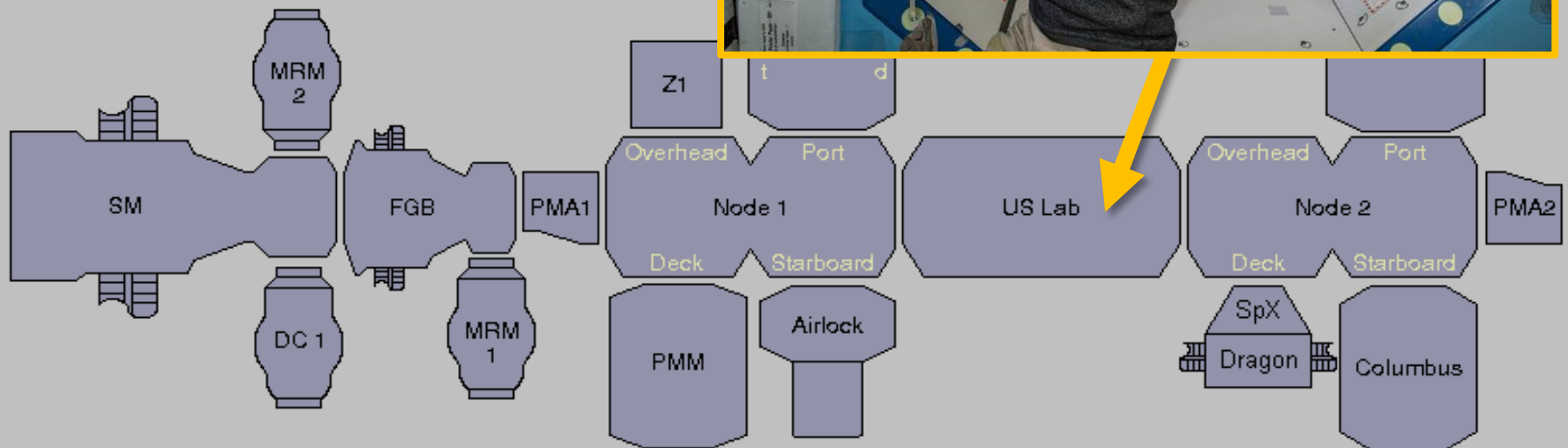


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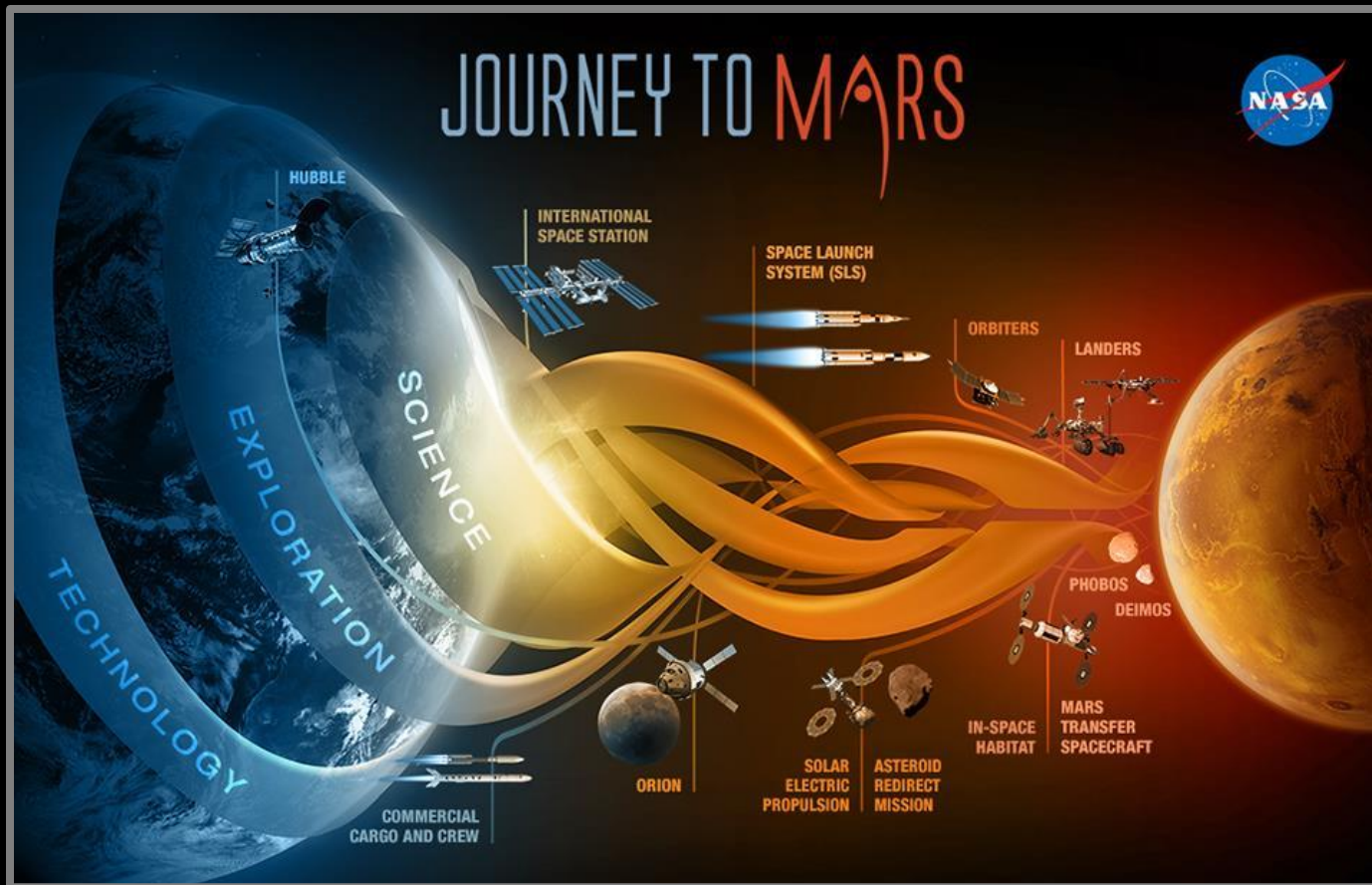




Background: *U.S. Space Flight*

■ The Future...

- NASA to send humans to: An **asteroid** by 2025; **Mars** in the 2030s



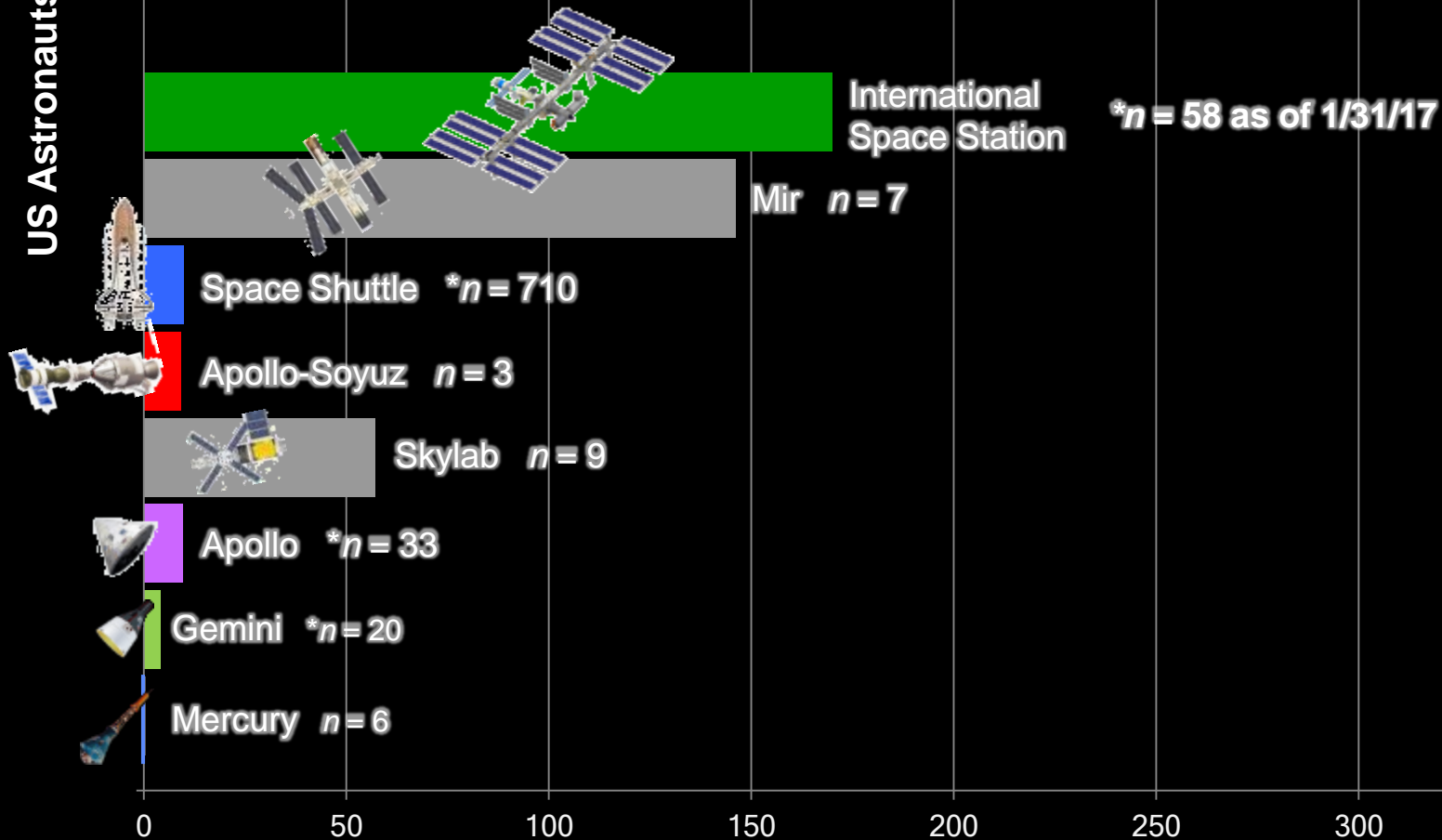


We are just entering, relatively speaking, the long-duration phase of space exposure...

Next Generation Missions



US Astronauts



Average Days

* Person-flights; may include multiple-time flyers w/in program



Background: *Physiological Challenges*

- **Physiological challenges** to astronauts are *substantial*, especially outside of Low Earth Orbit. For example...
- **Muscle Density & Function**
 - Impacted w/in days in space
 - During 2-wk Shuttle missions: reduction in fiber mass
 - Long-term space flight could result in ~40% loss in overall muscular function
 - Increased risk of injury
 - Impeded ability to operate spacecraft & equipment



Bone



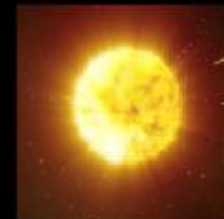
Sensory Motor



Muscle



Cardiovascular



Radiation



Exercise



Sleep Cycle



Food & Nutrition



Medical Care



Background: *Physiological Challenges*

- **Physiological challenges** to astronauts are *substantial*, especially outside of Low Earth Orbit. For example...
- *Muscle Density & Function*
- *Bone Health*
 - In space, bone density lost at ~24x the avg rate on Earth
 - Can lead to kidney stones, fractures, hip/spine problems, impaired healing



Bone



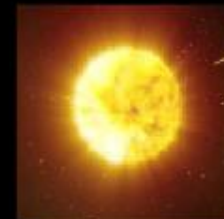
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Background: *Physiological Challenges*

- **Physiological challenges** to astronauts are *substantial*, especially outside of Low Earth Orbit. For example...
- *Muscle Density & Function*
- *Bone Health*
- *Ionizing (High Energy) Radiation*
 - Filtered by Earth's magnetic field
 - Galactic cosmic radiation
 - Bare atomic nuclei (as heavy as iron atoms) traveling at speed of light
 - Mars mission may expose ~90x the max *annual* dose recommended on Earth
 - Cataracts??
 - Solar flares
 - Can produce unexpected, lethal radiation spikes



Bone



Sensory Motor



Muscle



Cardiovascular



Radiation



Exercise



Sleep Cycle



Food & Nutrition



Medical Care



Background: *Physiological Challenges*

- **Physiological challenges** to astronauts are *substantial*, especially outside of Low Earth Orbit. For example...
- **“Vision Issues”**
 - For >40 yrs, anecdotal reports indicated VA impairments w/ spaceflight
 - NASA survey (n > 300) showed **29%** of short- & **60%** of long-duration (ISS) crew experienced “degradation” of dist or near VA
 - Some ISS cases did not resolve post-flight
 - In 2005, a more serious disorder was identified. Termed:
 - Vision Impairment Intracranial Pressure (VIIP) --or--
 - Microgravity Ocular Syndrome (MOS)





VIIP/MOS Clinical Findings





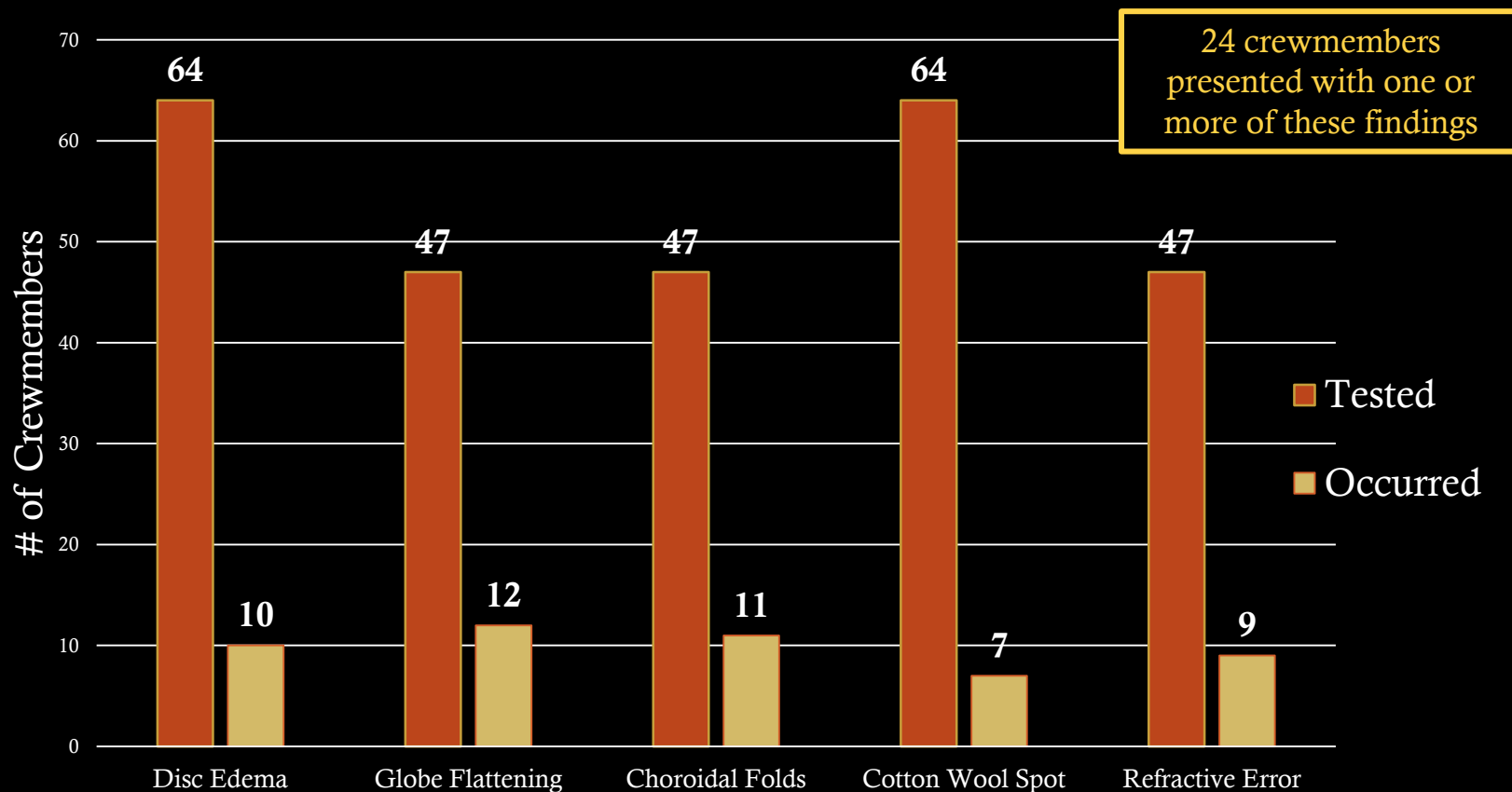
VIIP/MOS: Clinical Findings

To date, 24 USOS ISS long-duration spaceflight astronauts have developed some or all of the following findings:

- Ocular* {
 - Hyperopic shift
 - Globe flattening
 - Choroidal folds
 - Cotton wool spots
 - Optic disc edema
 - Optic nerve sheath distention} *ALL are potential signs of elevated intracranial pressure (ICP)*
- Mildly elevated post-flight intracranial pressure
 - 21 - 29 cm H₂O range
 - Upper limit of normal: ~20 cm H₂O
 - Gray zone: 20.1 – 24.9 cm H₂O



USOS Individuals w/ VIIP/MOS Findings: Expeditions 1-48



❖ Disc Edema = Modified Frisen Scale Grade ≥ 1 at first post-flight eye exam (via fundoscopy)

❖ Globe Flattening = A change compared to preflight (via MRI or ultrasound)

❖ Choroidal Folds = New or worsened compared to pre-flight (via OCT)

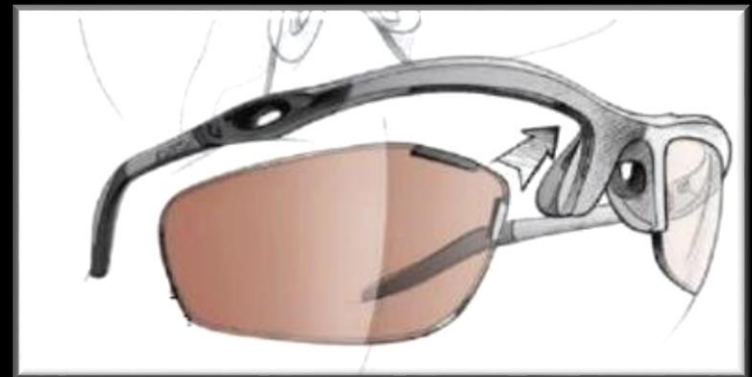
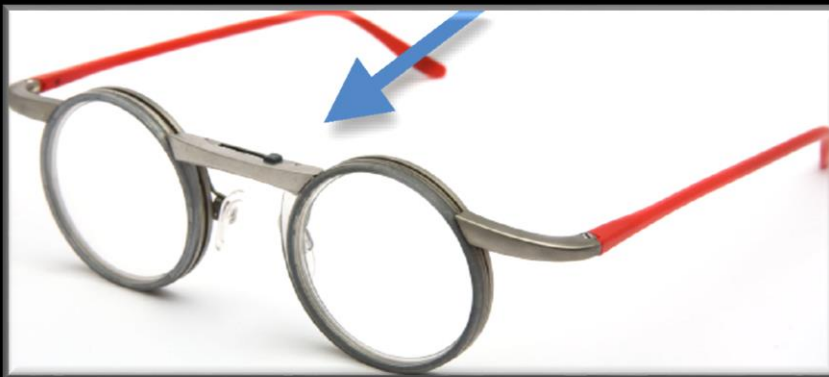
❖ Cotton Wool Spot = Presence in-flight or post-flight (via fundoscopy)

❖ Refractive Error = Change in cycloplegic (spherical) refraction $\geq 0.75D$ from preflight to first post-flight eye exam



Clinical Findings: *Hyperopic Shift*

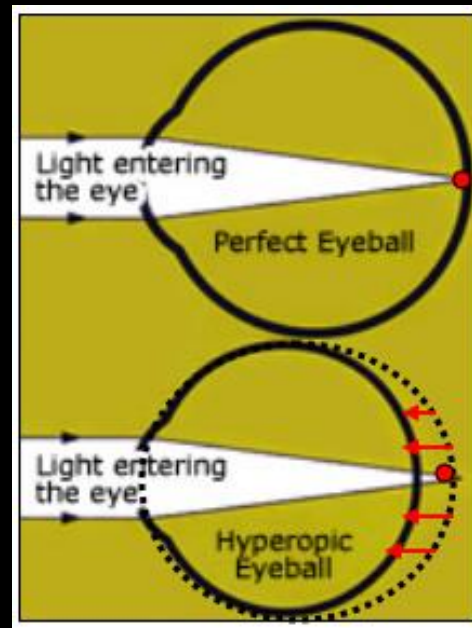
- Of the active astronaut population...
 - 80% wear vision correction (32% contact lenses)
 - Mean age = 47 yrs
 - Majority are presbyopic (i.e., a normal, age-related, progressively worsening inability to focus clearly on near objects)
- From postflight questionnaires (1989 - 2011): 29% of short-duration (Shuttle) & 60% of long- duration (ISS) mission astronauts report a *subjective degradation in vision*, especially at near
 - Provided “Space Anticipation Glasses”





Clinical Findings: *Hyperopic Shift*

- Subjective Degradation in Vision (cont):
 - Associated w/ *Hyperopic Shifts* in refractive error due to *Globe Flattening*
 - A 1 mm decrease in axial length will produce a ~2.7 diopter hyperopic shift
 - **Largest shift to date is +1.75 diopters**
 - In presbyopes: Typically decreases near visual acuity (VA), but leaves distant VA intact



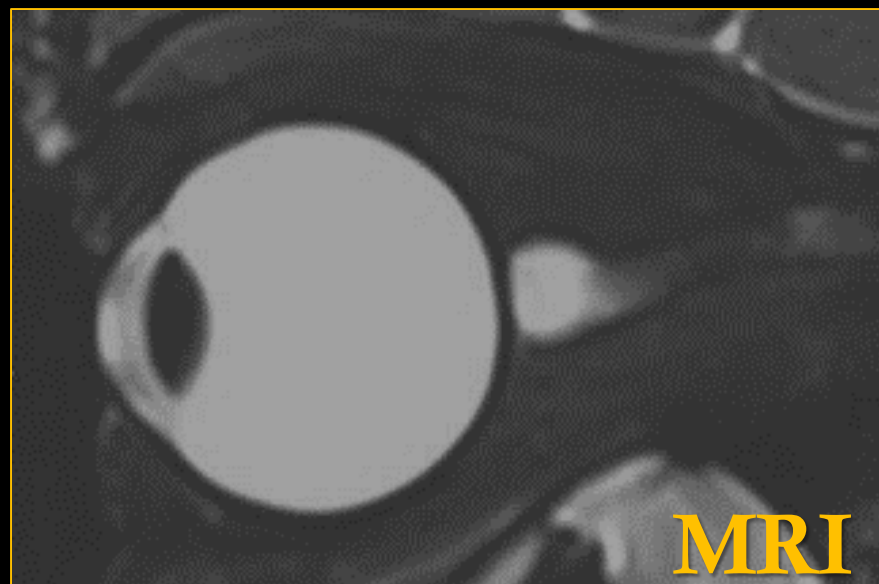


Clinical Findings: *Globe Flattening*

■ Case Example:

- Male, mid 40s at time of flight
- No significant PMH/PSH/PFH
- No meds
- Normal BP (118/64)
- Normal lipids
- ECG Stress test normal
w/ VO_2 max of 51ml/kg

- *Terrestrially*: Globe flattening associated w/ papilledema (i.e., disc edema 2° to increased intracranial pressure); typically bilateral



Pre-flight

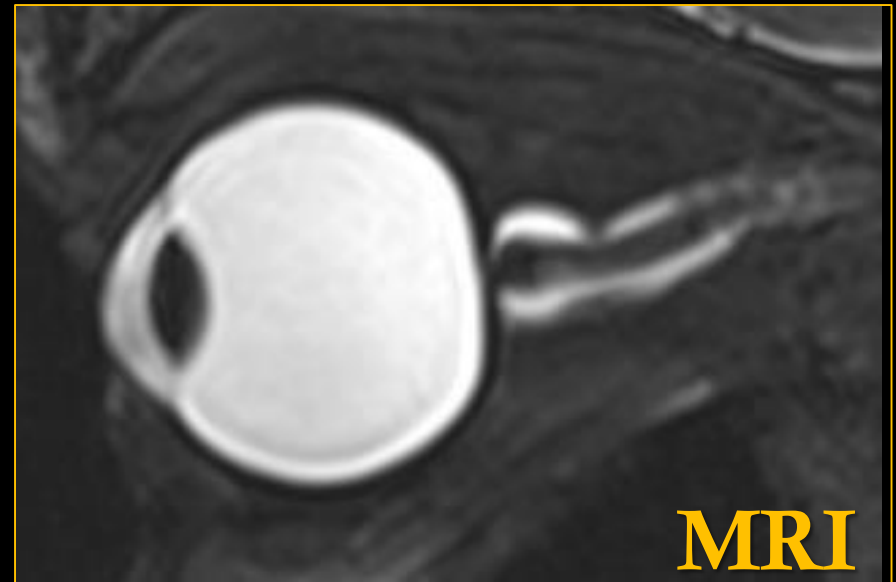


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6 days post-flight

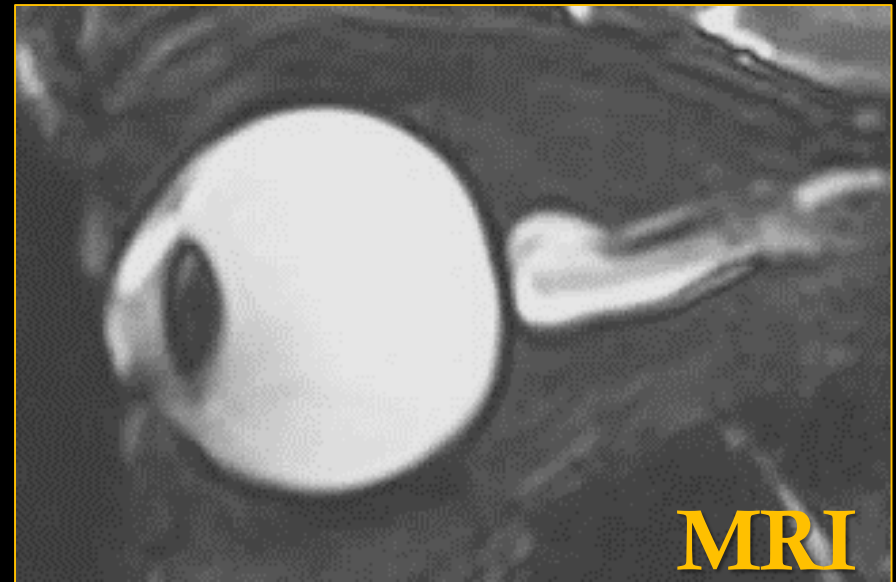


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1 year post-flight

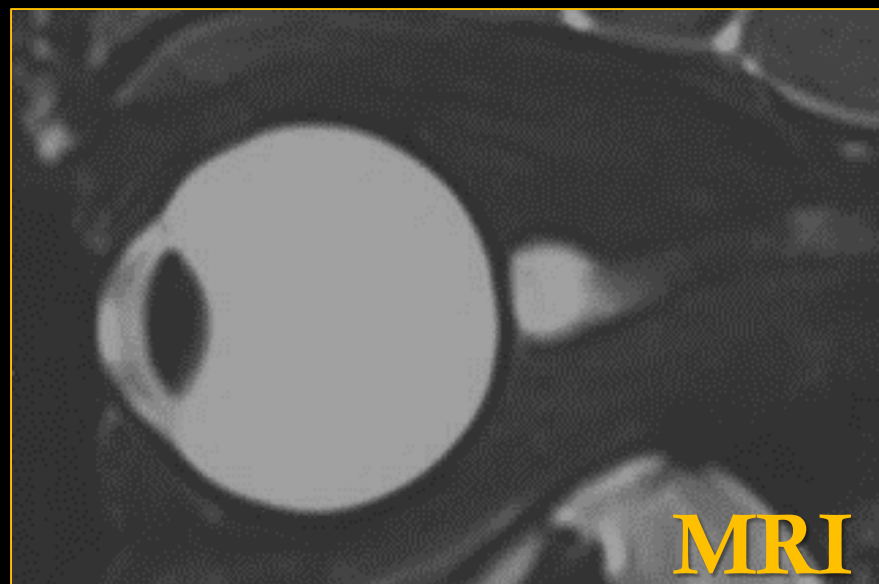


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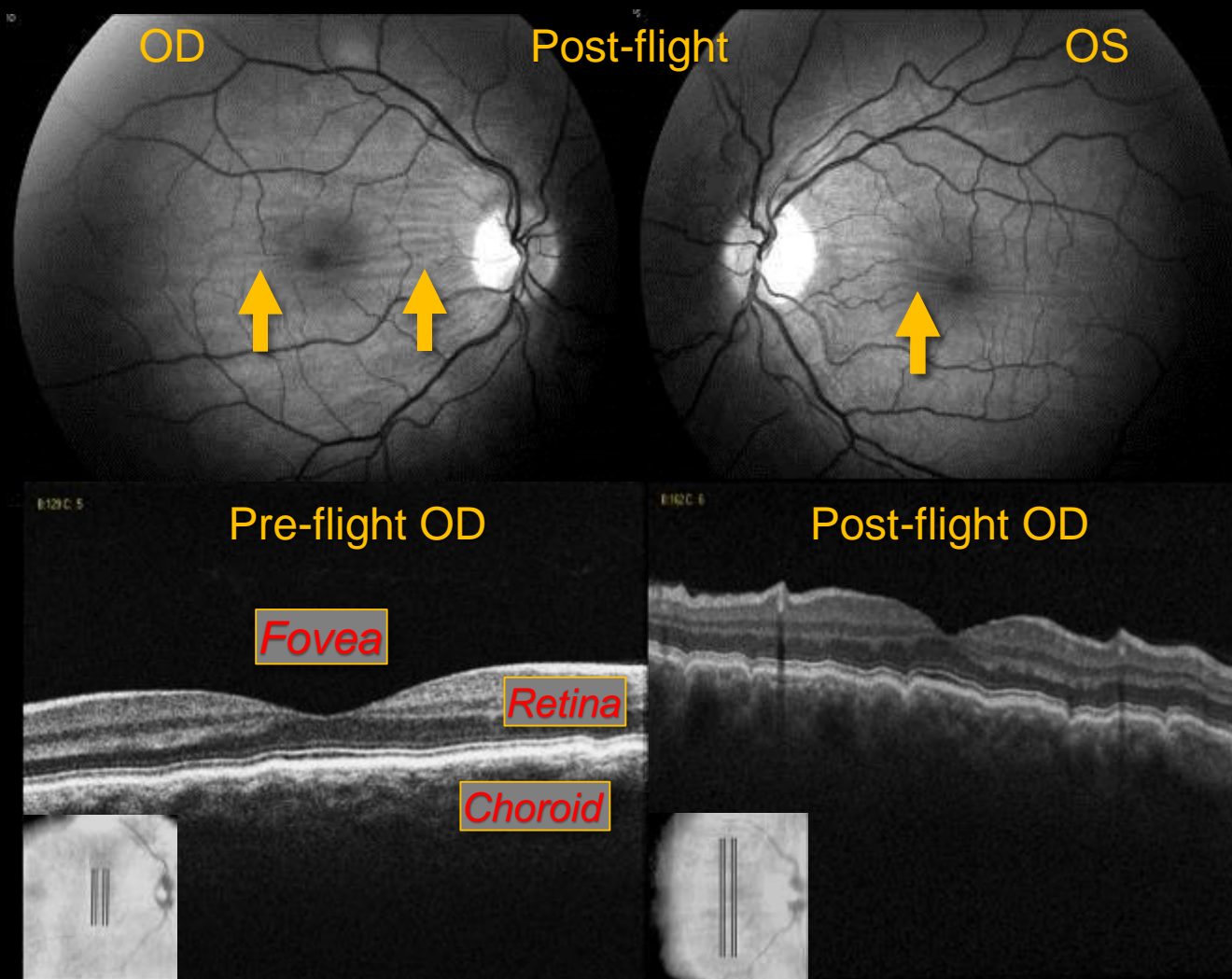
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Pre-flight



Clinical Findings: *Choroidal Folds*



- Choroidal thickening due to vessel engorgement → induces choroidal (and sometimes retinal) folds
- Can resolve post-flight or can persist (for 5+ yrs)
- So far, no clinically-significant impact on BCVA
- *Terrestrially: Assoc. w/ choroidal tumors, scleritis, retrobulbar mass, papilledema/IIH*



Clinical Findings: *Cotton Wool Spots*

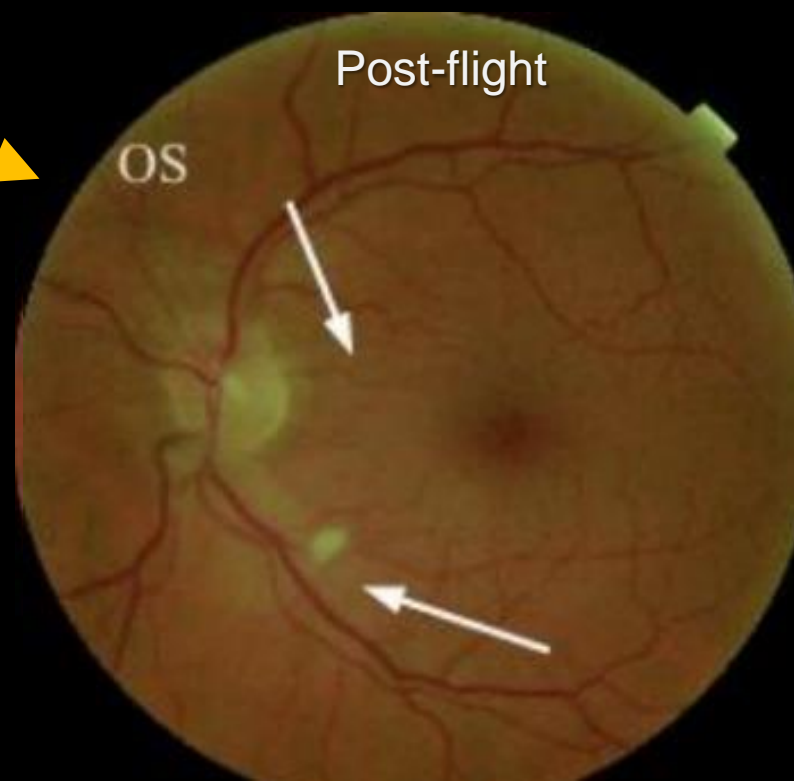
Posterior pole fundoscopic images
OD & OS for two ISS crewmembers

- Top arrows: **Choroidal folds**
- Bottom arrows: **Cotton wool spots**

■ Cotton wools spots

- Abnormal retinal finding
- Accumulations of axoplasmic material w/in retinal nerve fiber layer
- Caused by ischemia → reduced axonal transport → swelling of axon → damaged nerve fibers
- *Terrestrially: Associated w/ diabetes, HTN, central retinal vein occlusion*

Example 1





Clinical Findings: *Cotton Wool Spots*

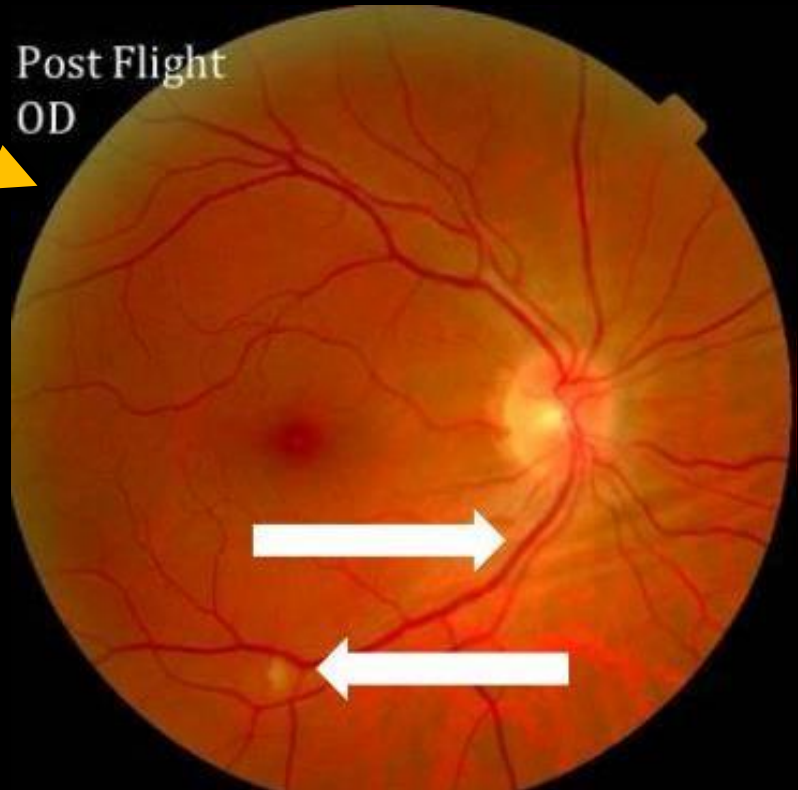
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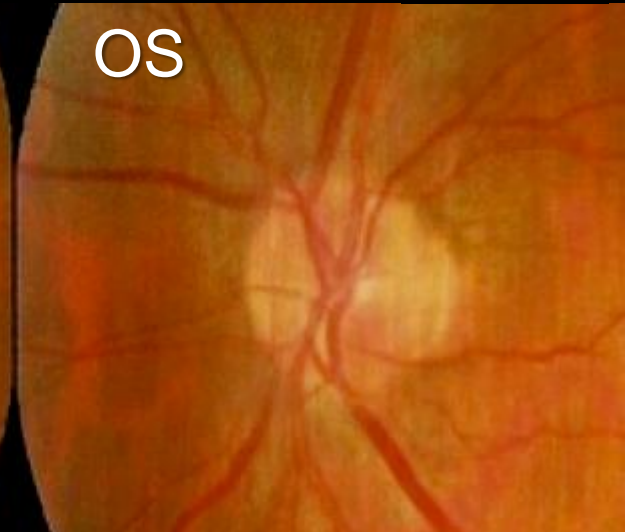
Example 2



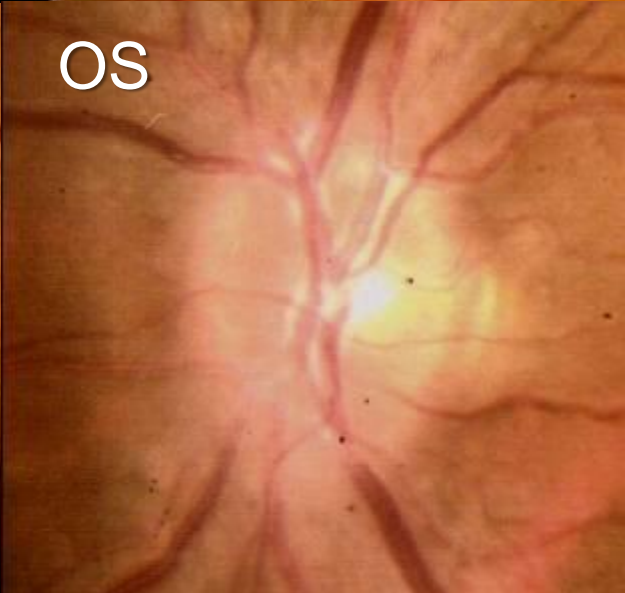


Clinical Findings: *Optic Disc Edema*

Pre-flight fundoscopic images of the right (OD) & left (OS) optic discs



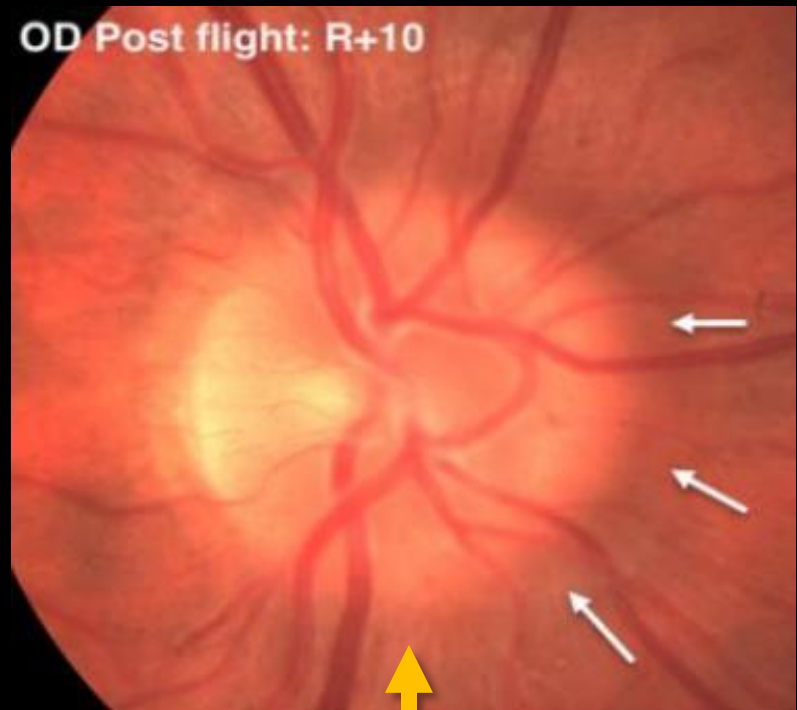
Post-flight images of optic discs, showing *Grade 3 edema OD & Grade 1 edema OS*





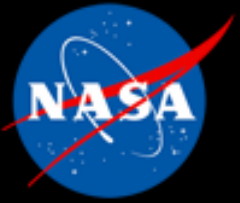
Clinical Findings: *Optic Disc Edema*

- *Terrestrially*: Optic disc edema is associated with:
 - Unilateral: Optic neuritis, optic neuropathy, retinal artery/vein occlusion
 - Bilateral: Increase in ICP...
 - IIH (→ “papilledema”)
 - Intracranial mass
 - Cerebral edema
 - Increased CSF production
 - Decreased CSF absorption
 - Obstructive hydrocephalus
 - Venous outflow obstruction
 - Typically reduces VA, enlarges blind spot, causes relative afferent pupillary defect & color impairment



Fundoscopic image of optic disc OD,
10 days after return to Earth

- Arrows: “C” shaped halo of edema



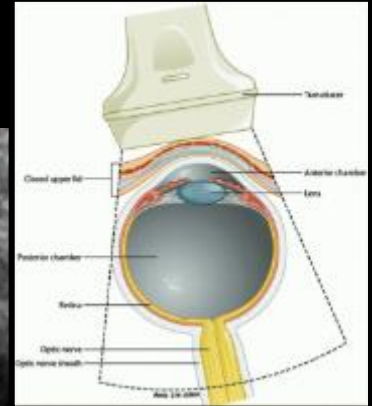
Clinical Findings: *Optic Nerve Sheath Distention*

Post-flight ultrasound image of globe, optic nerve (ON; purple), and optic nerve sheath (green). Showing:

- ON Sheath distention
- ON tortuosity

Post-Flight OD

12 mm



- ON Sheath *terrestrially*:
 - Normal diameter (ONSD) < 5.9 mm
 - Enlargement typically associated w/ increased ICP



Common Characteristics of the Cases





Common Characteristics of the Cases

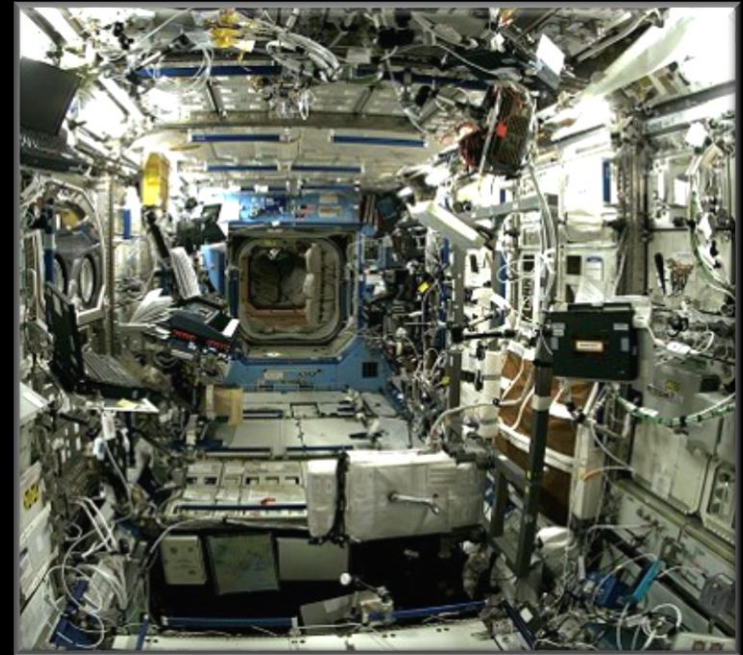
- Almost all were *~6 month duration ISS mission crewmembers*
 - One short-duration case w/ subtle disc edema (discovered retrospectively)
 - Severity related to flight duration?
 - What about a *3-yr Mars mission??*
- All had normal pre-flight eye exams
- Normal past medical history:
 - *Negative* for systemic disease
 - None had used medications before/during their mission that could increase ICP (e.g., vitamin A, tetracycline, corticosteroids, or nalidixic acid)





Common Characteristics of the Cases

- None complained of headaches, transient vision obscurations, double vision, pulsatile tinnitus, or vision changes during eye mvmts (i.e., classic symptoms of idiopathic intracranial hypertension)
- None experienced loss in BCVA, color vision, or stereopsis
- OD affected more than OS *in all cases*. If only one eye affected, always OD
- ISS cabin
 - Normal pressure & oxygen
 - Elevated CO₂
 - ~0.33-0.5% avg, w/ avg peak ~0.7%
 - 10x terrestrially: ~0.03-0.04%





Why is this Happening?



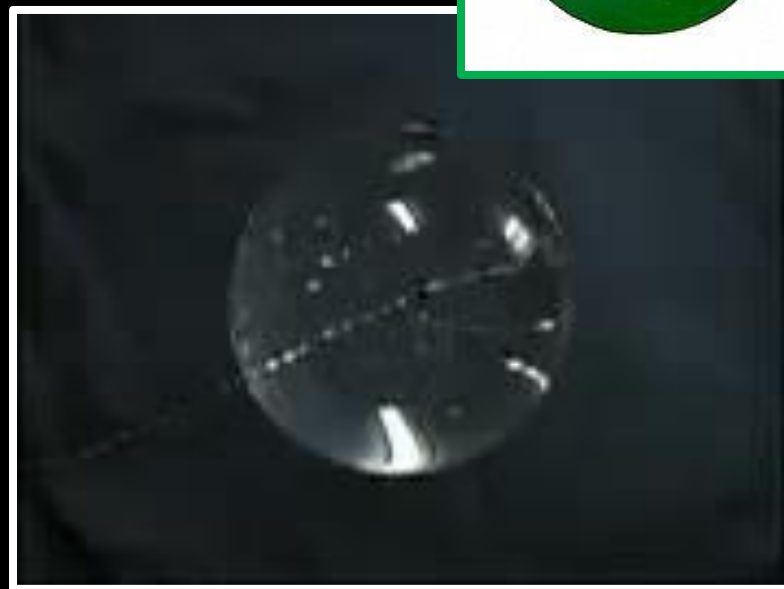


Why is this Happening?

- Terrestrially → Fluid is pulled downward by gravity (i.e., hydrostatic pressure)
- Microgravity → Fluid is free to uniformly distribute (i.e., hydrostatic pressure is eliminated)

Consider how hydrostatic pressure affects fluid/blood distribution in humans...

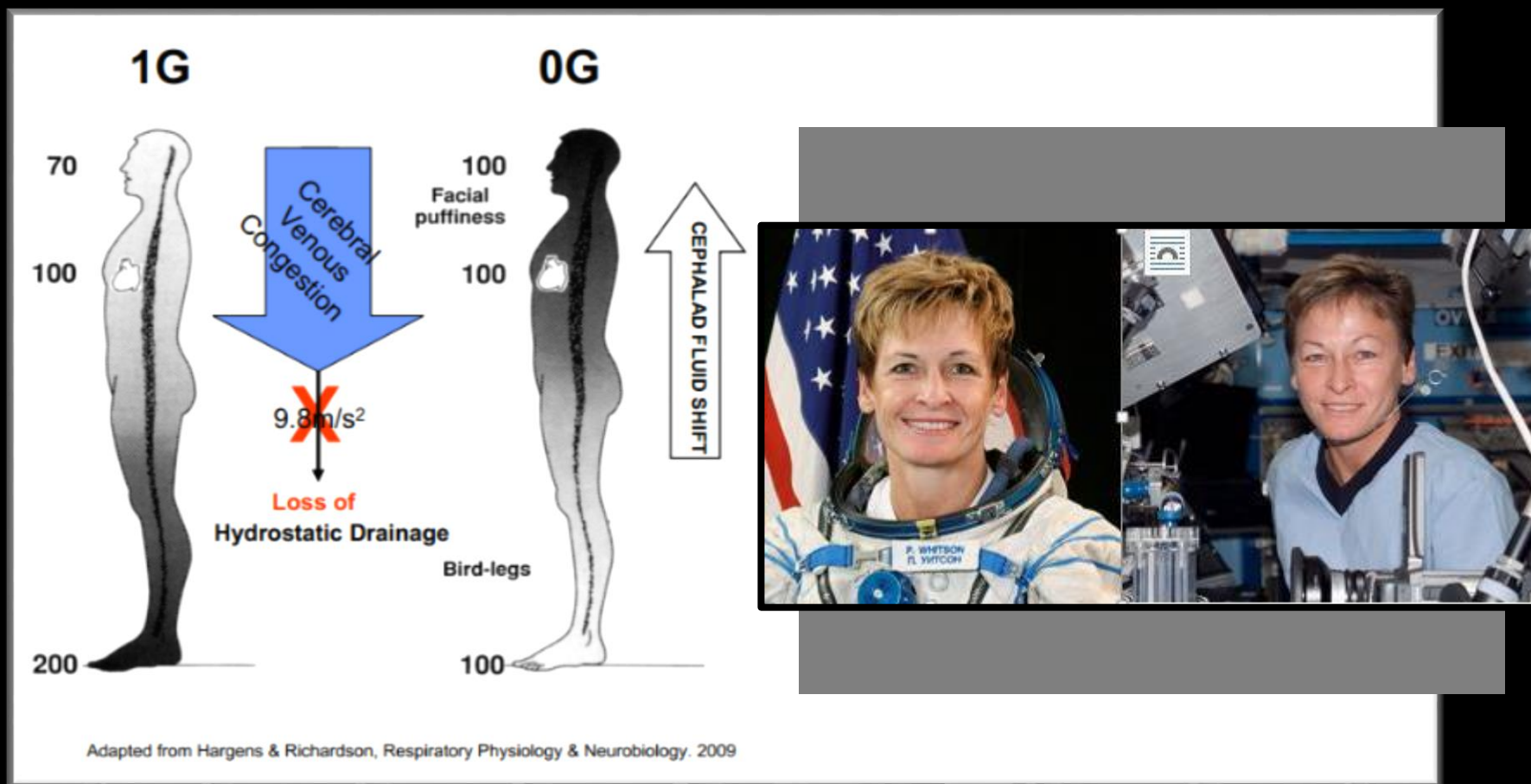
And what happens in its absence...





Why is this Happening?

Microgravity → Cephalad fluid shift → Cerebral venous congestion



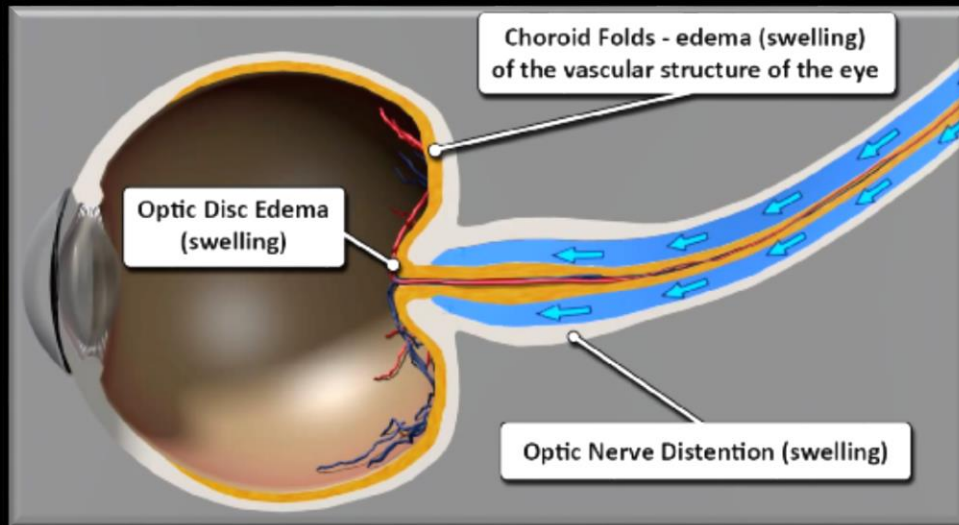


Why is this Happening?

- Current Risk Statement:

“Visual Impairment Intracranial Pressure” (VIIP)

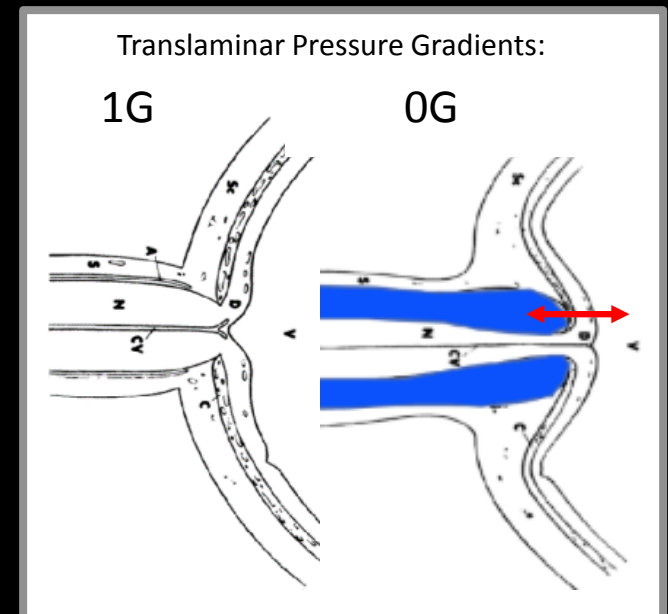
"Given that the microgravity environment causes cephalad fluid shift in astronauts, there is a probability that astronauts will have intracranial hypertension (IHT) to some degree, which if left untreated, could lead to deleterious health effects."





Why is this Happening?

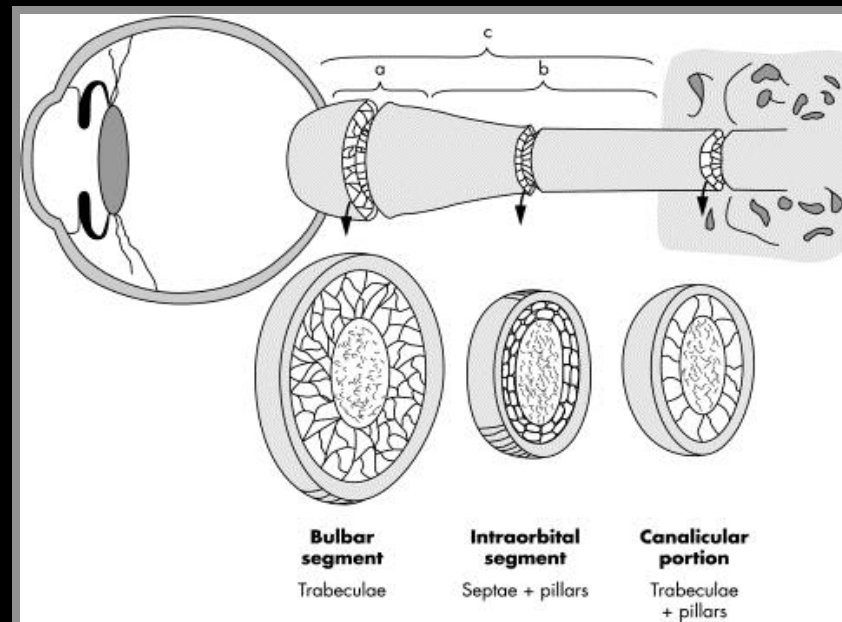
- Hypothesis #1: **Increased intracranial pressure**
 - The original theory, hence “Visual Impairment Intracranial Pressure”
 - Support:
 - Optic nerve edema & ONSD distention
 - Lateral & 3rd ventricle enlargement (like hydrocephalus) post-flight
 - Crowding of superior sagittal sinus post-mission
 - However:
 - Signs often unilateral & right-biased
 - If ICP increases, may increase only modestly
 - Globe flattening & choroidal folds can persist for years post-flight, despite a return to normal ICP





Why is this Happening?

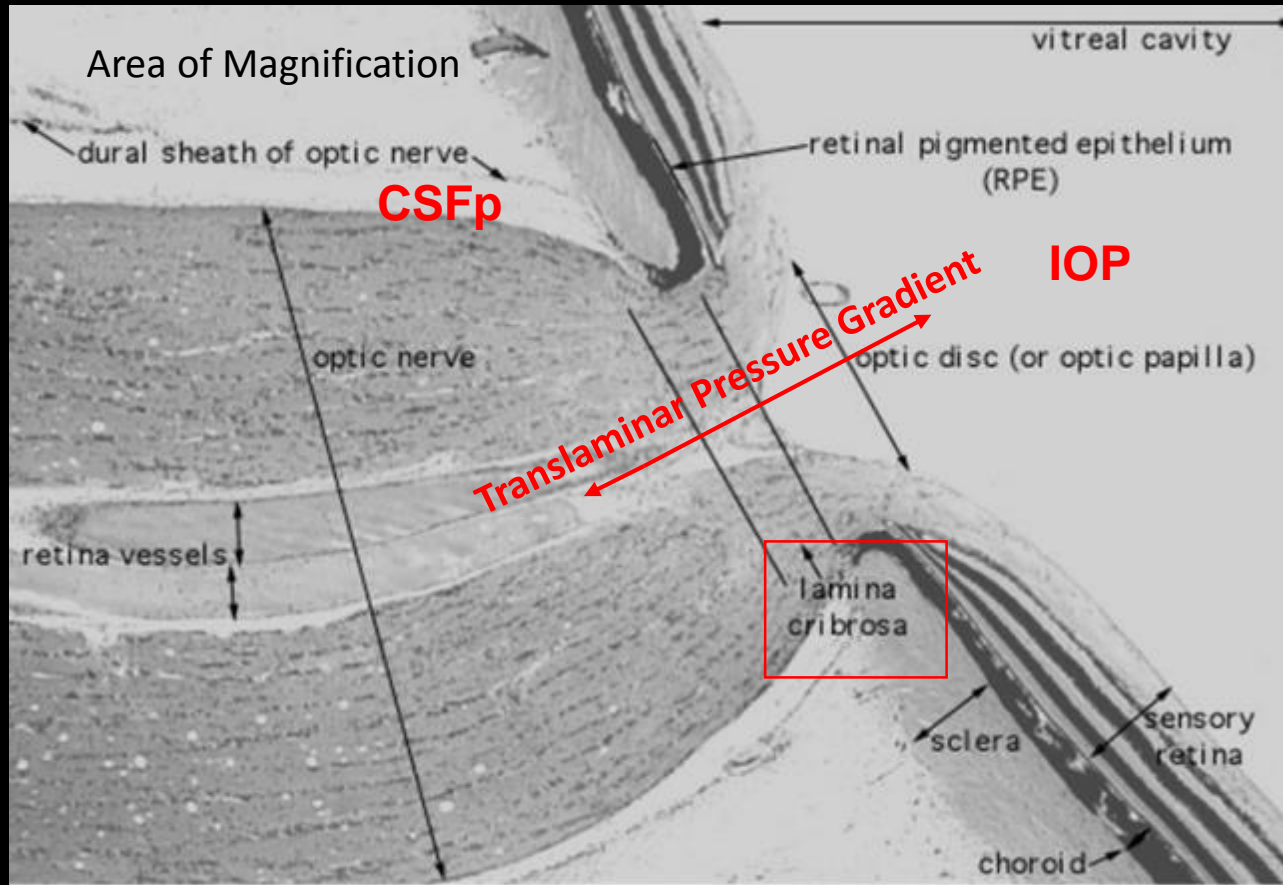
- Hypothesis #2: **This is a local ocular eye problem**
 - CSF cul-de-sac bathing ON might act as one-way valve for CSF flow during spaceflight → may increase local ICP around ON





Why is this Happening?

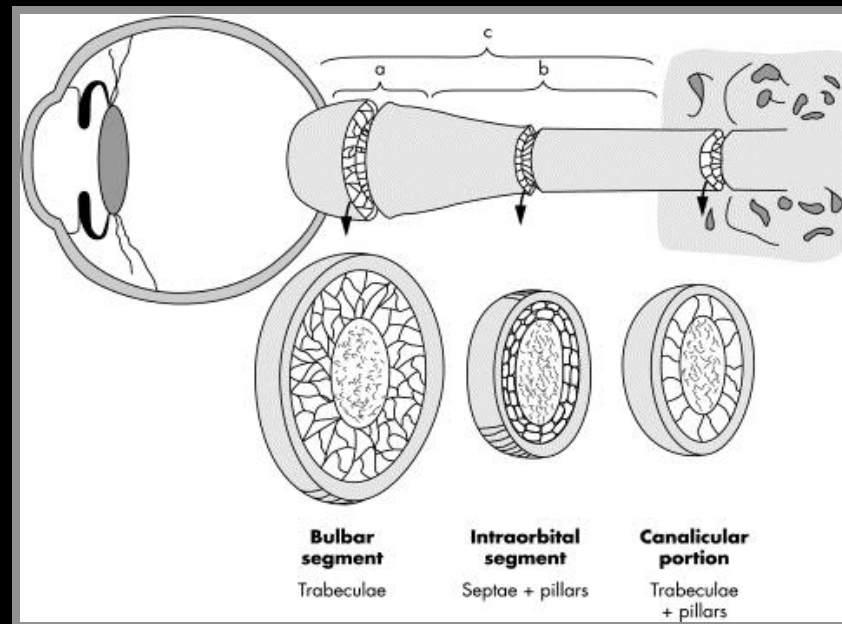
- Hypothesis #3: Slight IOP reduction + slight ICP increase
 - Variation of original VIIP theory (i.e., \uparrow ICP)





Why is this Happening?

- Hypothesis #4: **Individual anatomical or genetic factors**
 - For example: VIIP may be associated w/ atypical folate-dependent 1-carbon metabolic pathway in some astronauts
 - May increase local toxin concentration w/in ON sheath





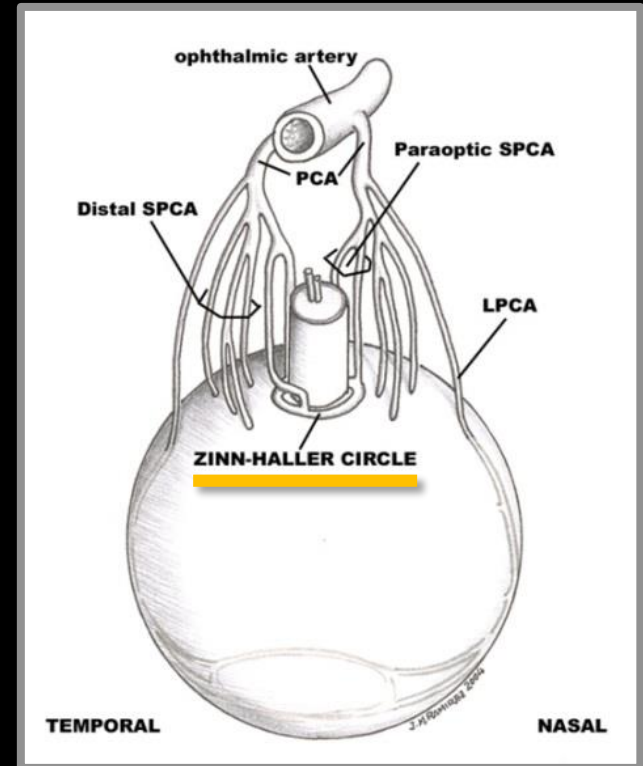
Why is this Happening?

- Hypothesis #5: Vessel congestion places local pressure in choroid & around optic nerve (“Circle of Zinn-Haller” theory)

In μ Gravity, head venous pressure \approx 15-20 mmHg
(vs. standing terrestrially \approx -20 mmHg)

Choroid engorges & thickens,
even in non-VIIP cases

Choroidal blood supply forms an anastomosis around ON. If engorged & pressurized, may place *noose-like strain* around ON





In-flight Exacerbating Factors??

Resistive Exercise



High Oral Sodium Intake

Prepackaged Foods...

Up to 5000+ mg/day



High CO₂
~10x terrestrial levels



In-flight Pharmaceuticals





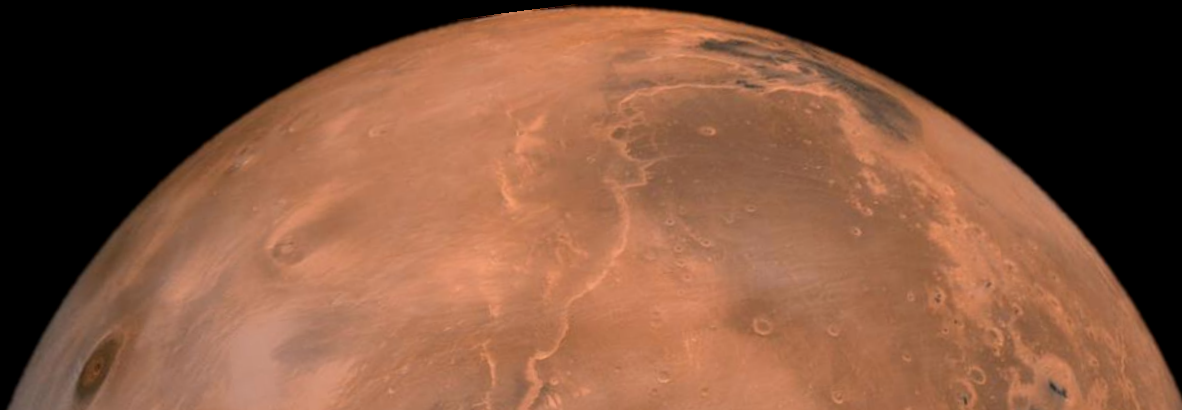
Medical Surveillance





Surveillance & Medical Data Collection

- 49 ISS expedition missions have been completed (since 2000)
- **Seminal VIIP case** occurred in **2005**
 - Choroidal folds & cotton wool spot OD; OS unremarkable
- Surveillance/medical data collection is ongoing and has evolved
 - Began *some* “VIIP” related testing in 2008 (w/ Exp 18)
 - Inconsistent testing until Feb 2010 (Exp 23) when standardized medical monitoring (i.e., “**Eye MED B**”) came into effect





Surveillance & Medical Data Collection

Terrestrially (pre- & post-flight)

- 3T MRI – Special “NASA Astronaut” protocol
- Comprehensive eye exam. *Highlights:*
 - Refraction (manifest & cycloplegic); Amsler
 - Threshold VFs; Contrast sensitivity
 - Optical biometry; Applanation tonometry
 - Optical Coherence tomography (OCT)



On-Orbit

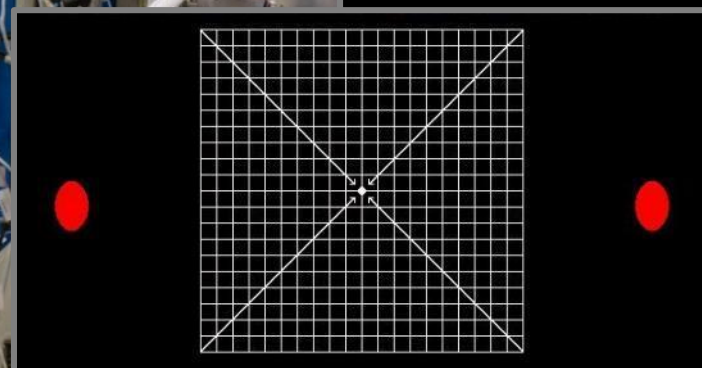
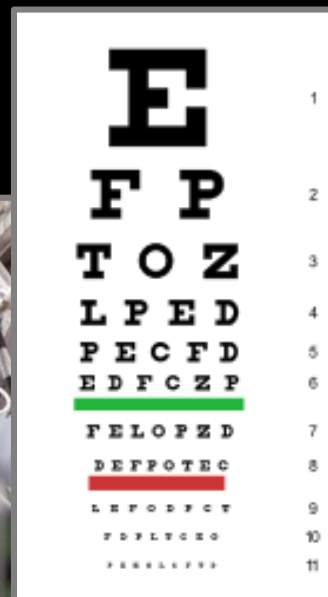
- Visual Acuity (Dist & Near)
- Amsler Grid
- Vision Questionnaire
- Ocular Ultrasound
- Fundoscopy
- OCT
- Tonometry (when clinically indicated)





Surveillance & Medical Data Collection

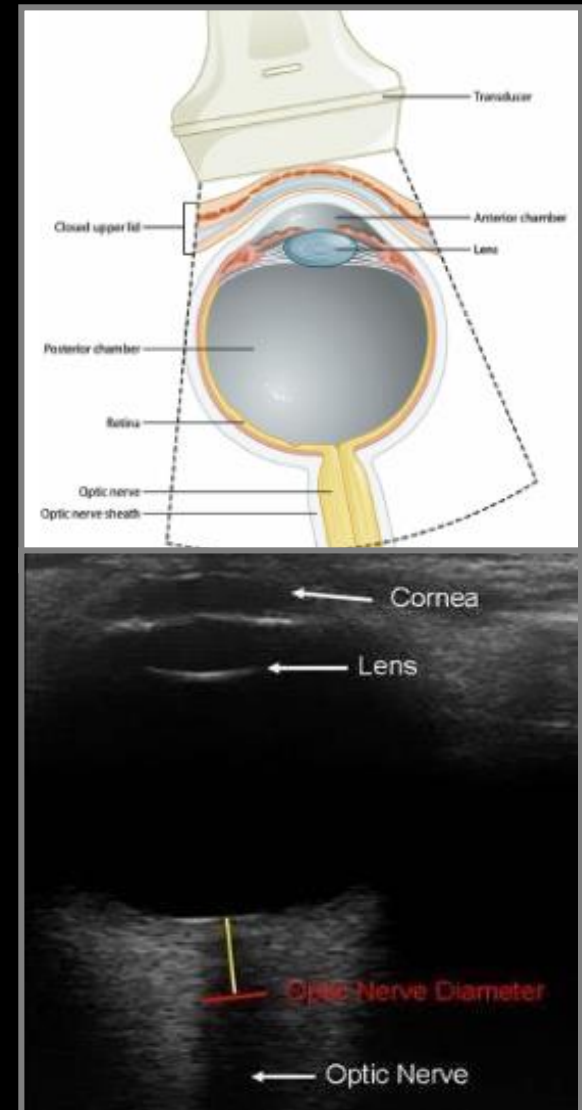
On-orbit Visual Acuity & Amsler Grid

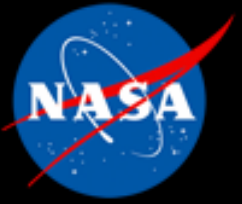




Surveillance & Medical Data Collection

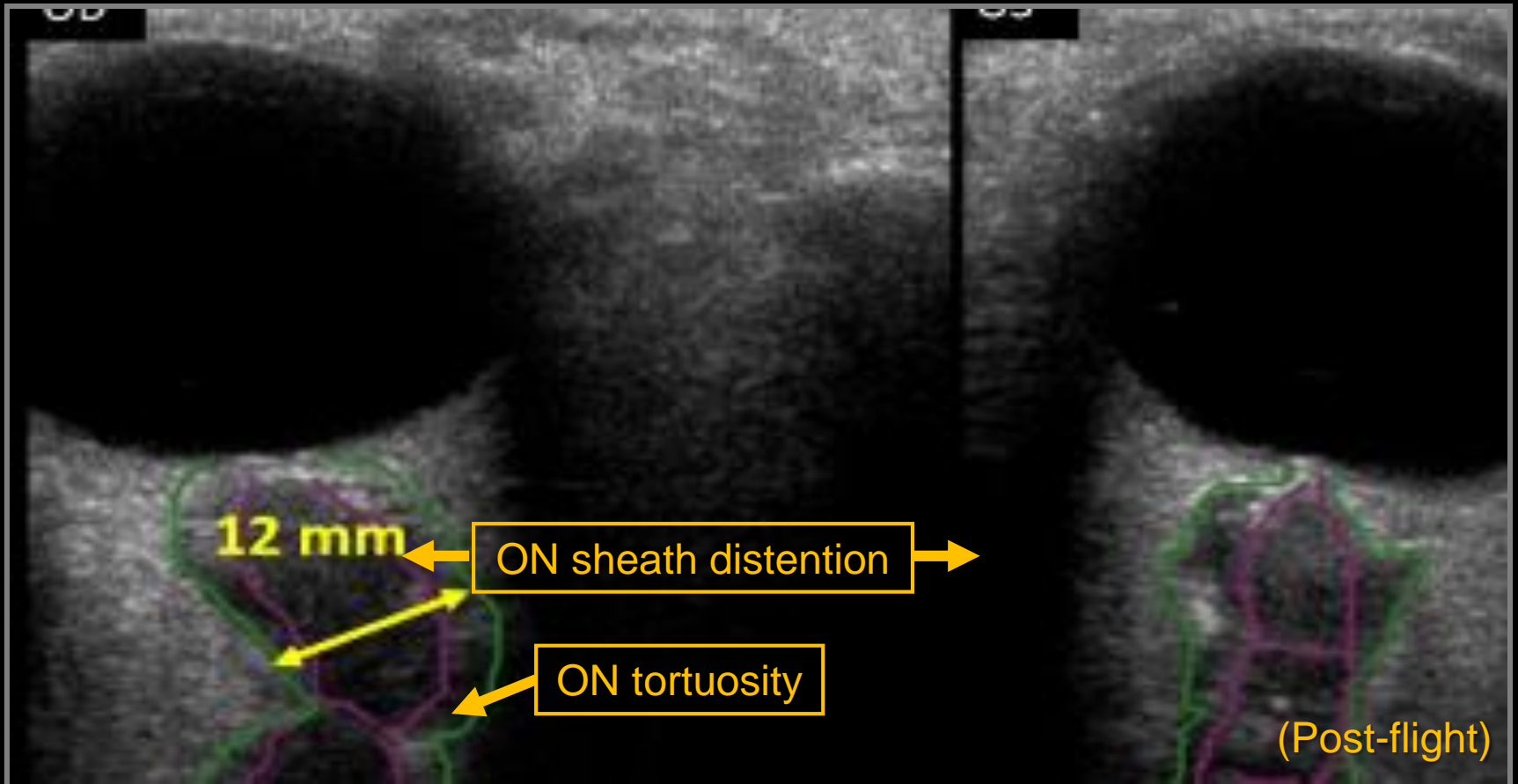
On-orbit Ultrasound Imaging





Surveillance & Medical Data Collection

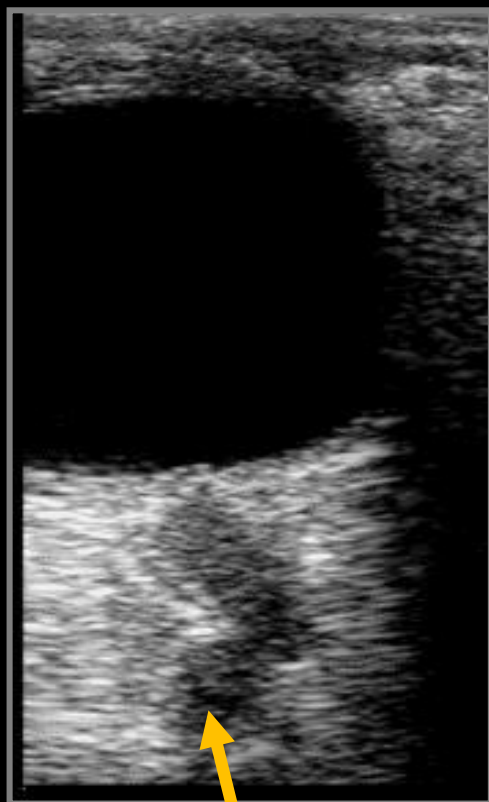
On-orbit Ultrasound Imaging





Surveillance & Medical Data Collection

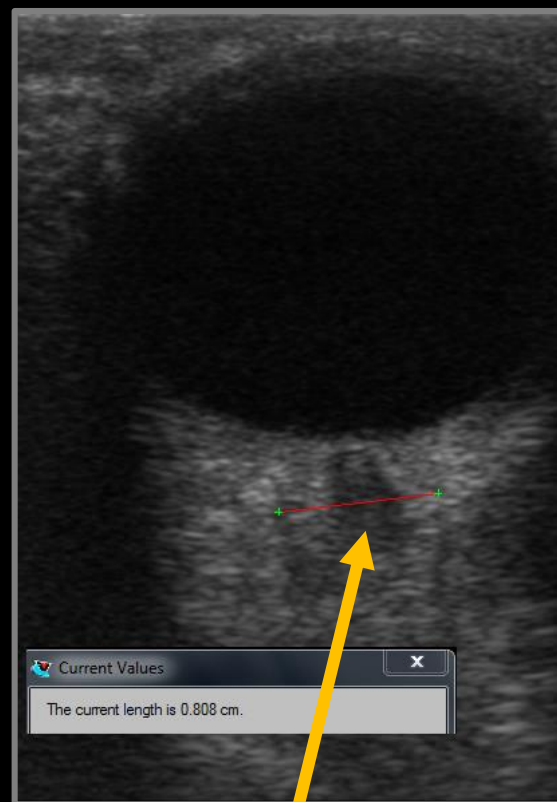
On-orbit Ultrasound Imaging



ON tortuosity



Elevated optic disc



ON sheath distention



Surveillance & Medical Data Collection

On-orbit Fundoscope





Surveillance & Medical Data Collection

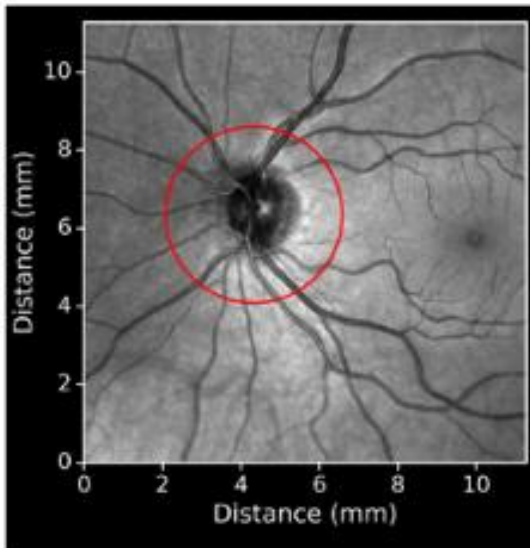
On-orbit Optical Coherence Tomography (OCT)



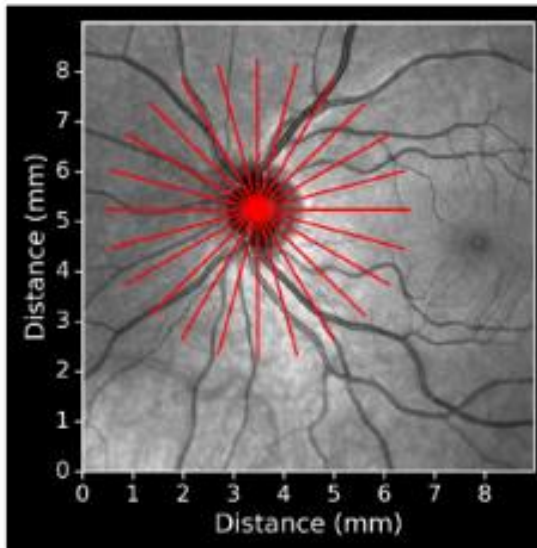


Nominal OCT Protocol

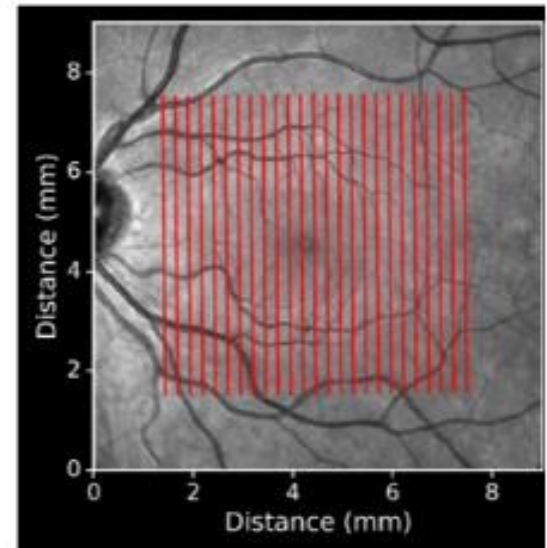
Circular ONH Scan



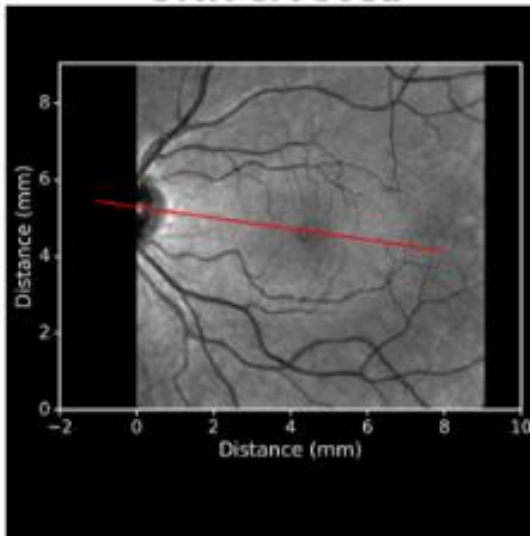
Radial ONH Scan



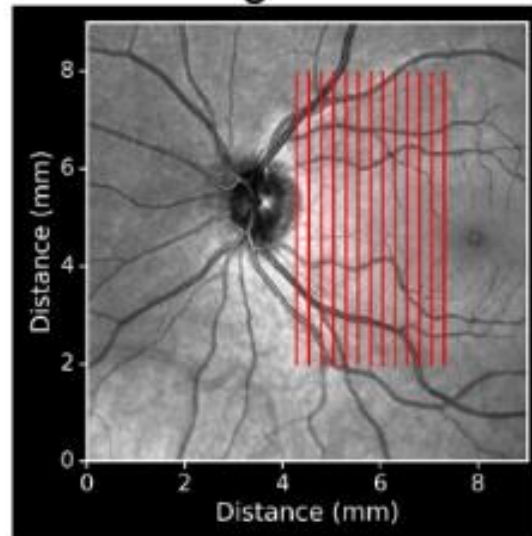
Vertical Macula Scan



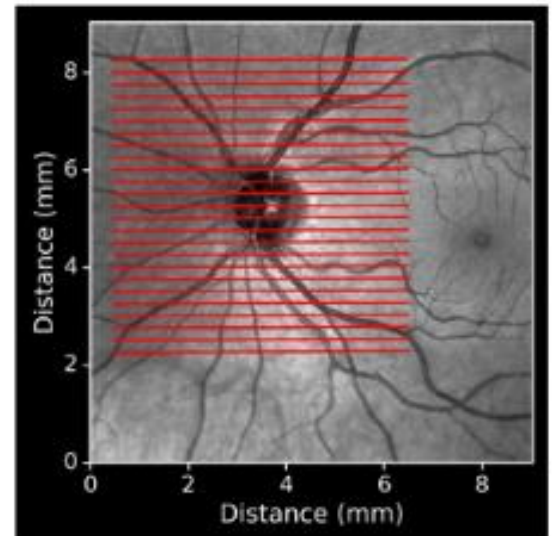
**Single Scan through
ONH & Fovea**

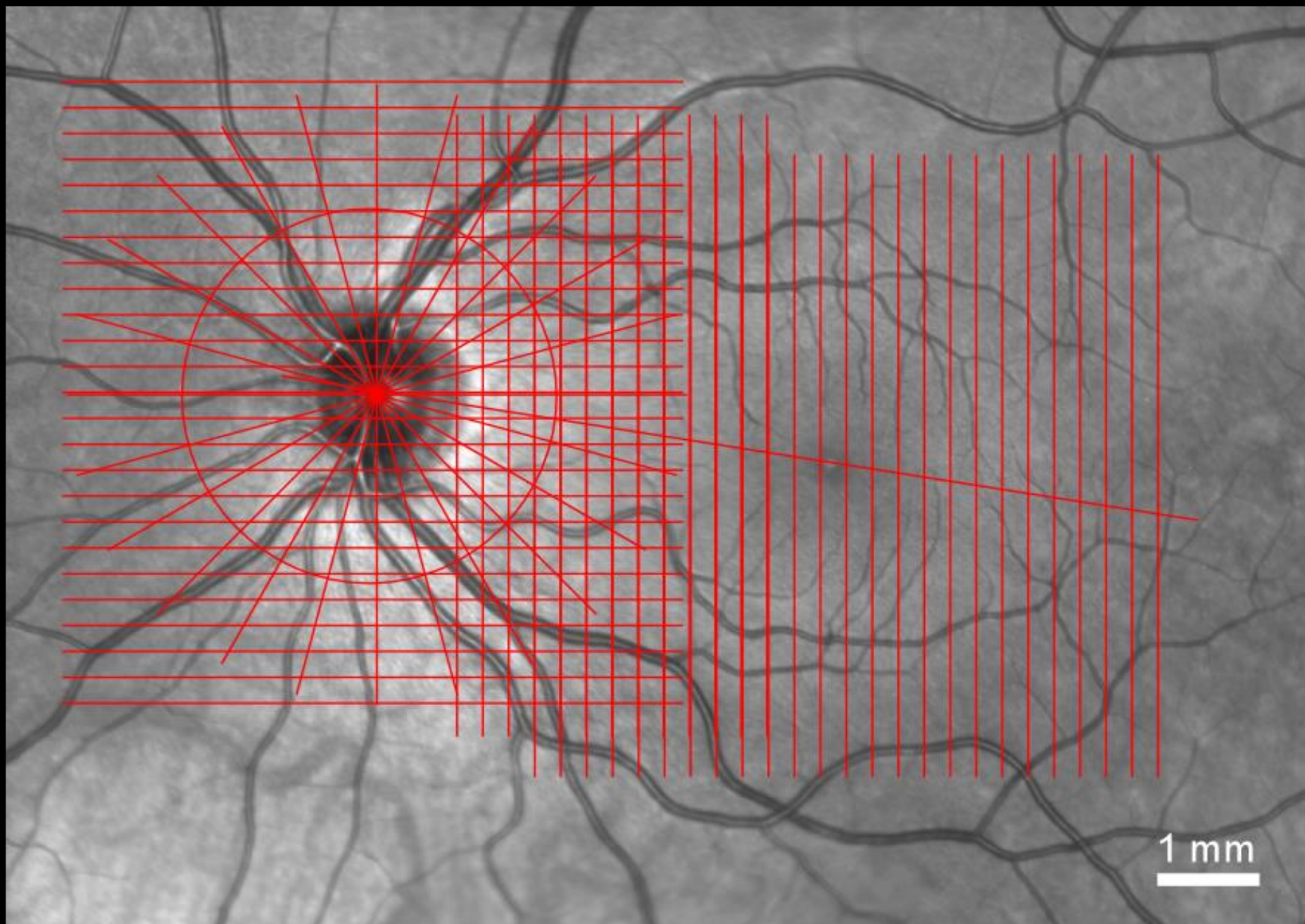


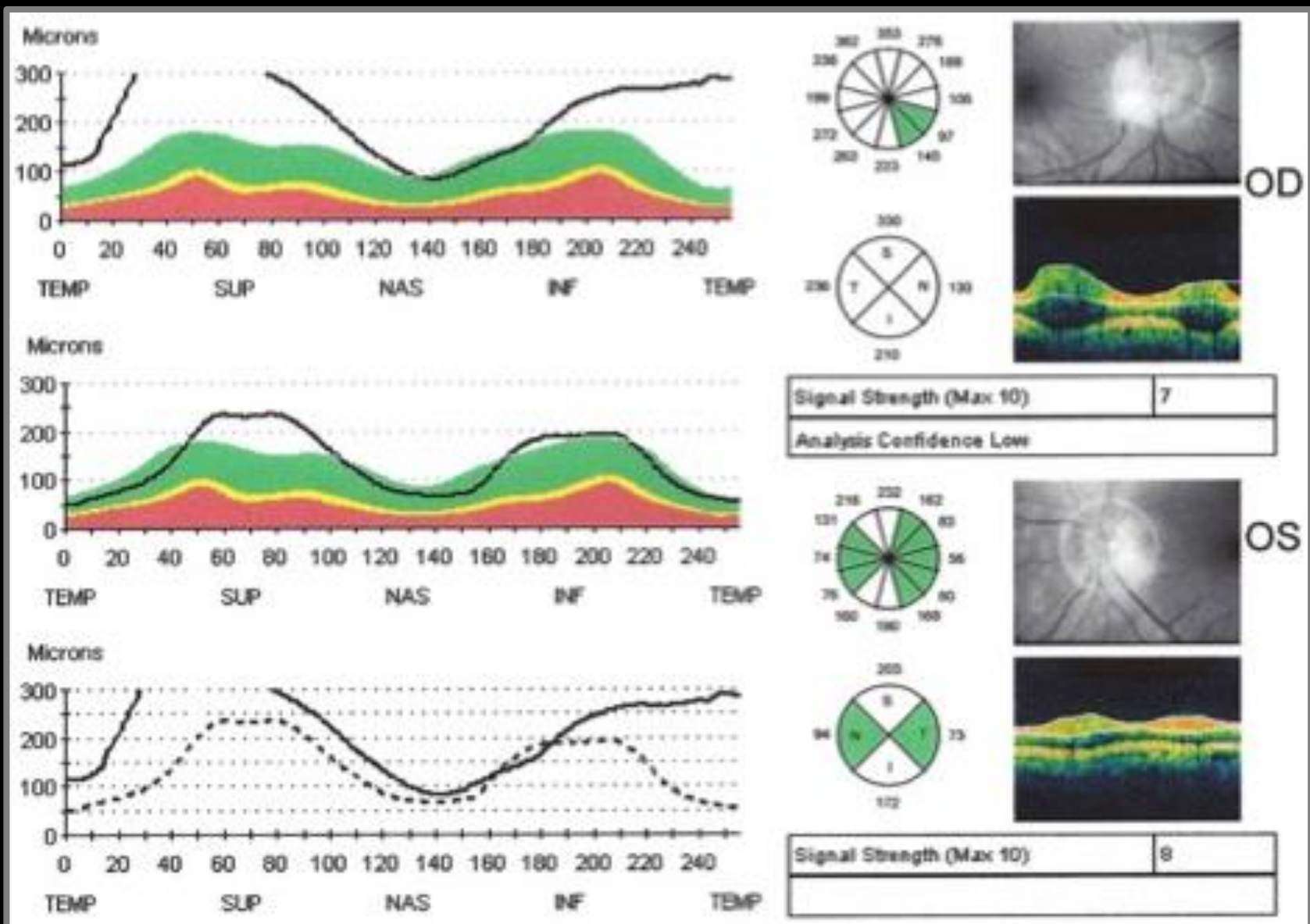
**Vertical Scan Between
Disk Edge & Fovea**



Horizontal ONH Scan





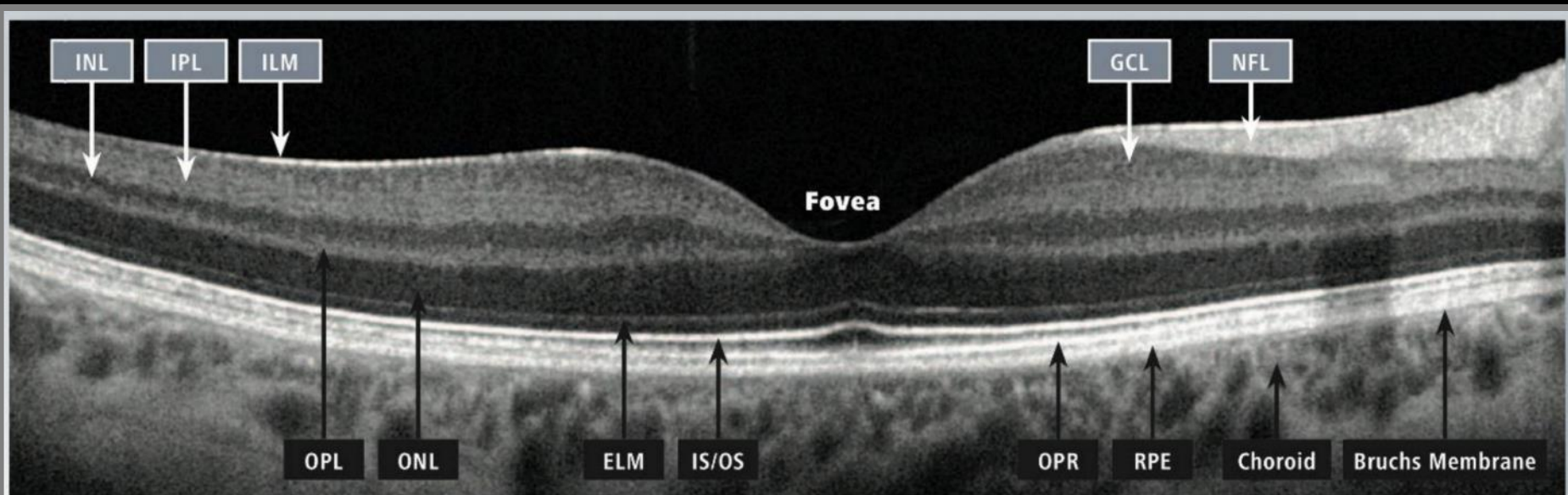


Post-flight OCT scan showing RNFL thickening consistent w/
observed optic disc edema OU



Surveillance & Medical Data Collection

On-orbit Optical Coherence Tomography (OCT)



ILM: Inner limiting membrane
IPL: Inner plexiform layer
INL: Inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer

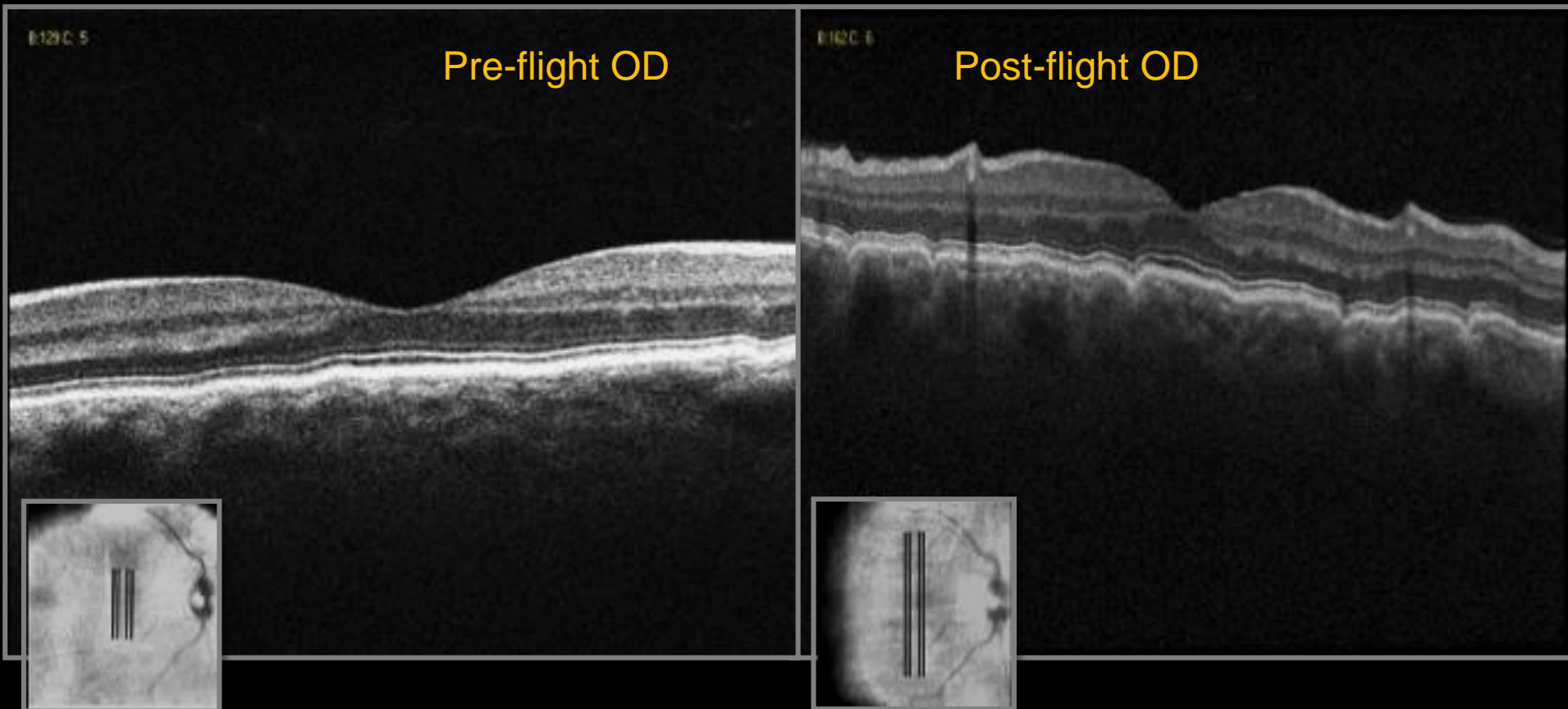
ELM: External limiting membrane
IS/OS: Junction of inner and outer
photoreceptor segments
OPR: Outer segment PR/RPE complex

NFL: Nerve fiber layer
GCL: Ganglion cell layer
RPE: Retinal pigment epithelium
+ Bruch's Membrane



Surveillance & Medical Data Collection

On-orbit Optical Coherence Tomography (OCT)





Surveillance & Medical Data Collection

On-orbit Tonometry





Clinical & Research Update

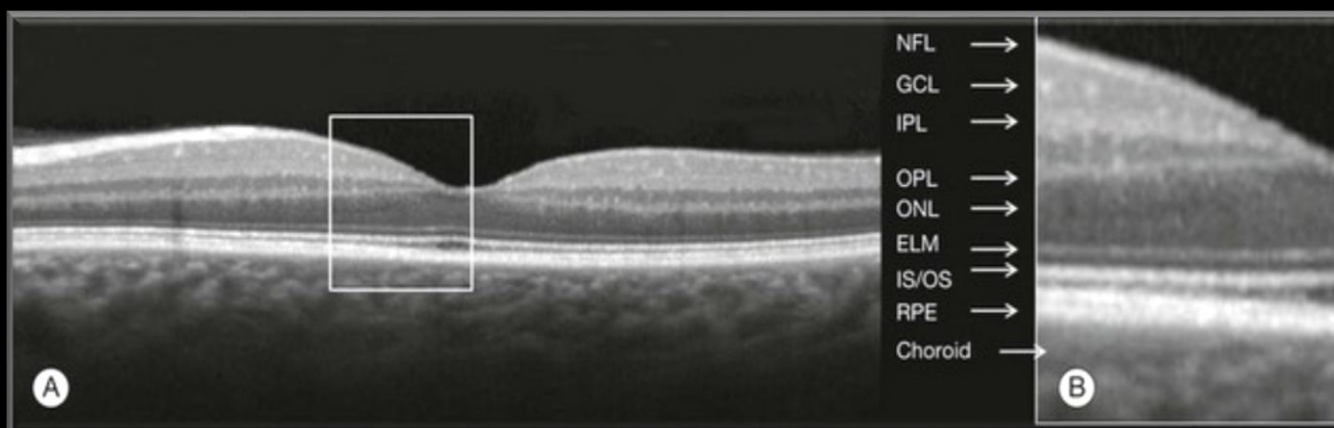




Clinical Update: Feb17

Ongoing clinical work

- Correlation between “**Form & Function**”: RNFL thickness changes (OCT) and their impact on visual sensitivity (VF)
- Correlations between VIIP/MOS signs and:
 - **Subcortical white matter hyperintensities** (WMH) found on MRI
 - **Cardiovascular parameters** (e.g., general fitness levels)
- Evaluation of **next-generation OCT** (“OCT2”): Will it enhance on-orbit imaging/data acquisition?





What We Are Watching Coming From Our Research Colleagues

- **Ocular Health Study & Fluid Shifts Study**
 - Both finish data collection in Summer 2017
- Clinical relevance of **MRI-based findings**
- Implementation of **direct ICP measures** (pre- & post-mission)
- Correlation btwn VIIP/MOS & **CO₂ using HDT (EnviHab)**





What We Are Watching Coming From Our Research Colleagues

- **Fluid Shifts Study:** OCT scan w/ lower body negative pressure
 - Not your typical clinical environment...!





Questions?

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